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SUPPORTING INFORMATION

Exploration of the nicotinamide-binding site of the tankyrases, identifying 3-arylisoquinolin-1-ones as potent and selective inhibitors

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Section A: General synthetic methods

Chemical reagents, solvents and starting materials were purchased from Sigma Aldrich, Goss Scientific, Alfa Aesar and Fisher Scientific and were used without further purification. Proton and carbon magnetic resonance spectra were recorded at 400.04 MHz or 500.13 MHz for ^1H NMR, at 100.59 MHz or 125.76 MHz for ^{13}C NMR and at 376 MHz for ^{19}F NMR, using CD_3OD , $(\text{CD}_3)_2\text{SO}$ and CDCl_3 , containing SiMe_4 as an internal standard. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60Å (particle size 40-63 μm). Most mass spectrometric data were obtained by means of electrospray ionisation using a microTOF instrument from Bruker Daltonics (Bremen, Germany) and calibrated using sodium formate solution. Melting points were obtained using a heated stage microscope (Reichert-Jung). Experiments were conducted at ambient temperature, unless otherwise noted. Solutions in organic solvents were dried with MgSO_4 . Pd_2dba_3 refers to tris(dibenzylideneacetone)dipalladium, SPhos refers to 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ refers to bis(triphenylphosphine)palladium(II) dichloride. The brine was saturated.

Section B: Experimental methods - chemical synthesis

5-Amino-3-(3-methoxyphenyl)isoquinolin-1-one hydrobromide (12e). Compound **31e** (31 mg, 110 μ mol) was stirred with HBr in AcOH (33%, 1.1 mL) at 65°C for 5 h. Evaporation yielded **12e** (29 mg, 73%) as a pale buff solid: mp 202-205°C; ^1H NMR (CD_3OD) δ 3.89 (3 H, s, Me), 6.13 (1 H, s, N-H), 6.95 (1 H, s, 4-H), 7.10 (1 H, dt, $J = 8.2, 0.6$ Hz, Ph 4-H), 7.35 (2 H, m, Ph 2,6- H_2), 7.46 (1 H, t, $J = 7.9$ Hz, Ph 5-H), 7.61 (1 H, t, $J = 7.9$ Hz, 7-H), 7.83 (1 H, dd, $J = 7.7, 1.0$ Hz, 6-H), 8.42 (1 H, d, $J = 8.1$ Hz, 8-H); ^{13}C NMR (CD_3OD) (HSQC / HMBC) δ 56.14 (Me), 98.49 (4-C), 113.73 (Ph 2-C), 116.98 (Ph 4-C), 120.39 (Ph 6-C), 127.56 (8a-C), 127.66 (4a-C), 127.82 (7-C), 128.96 (6-C), 129.47 (8-C), 131.60 (Ph 5-C), 134.01 (5-C), 136.68 (Ph 1-C), 144.29 (3-C), 161.82 (Ph 3-C), 164.54 (1-C); MS m/z 267.1115 ($\text{M} + \text{H}$) $^+$ ($\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_2$ requires 267.1135).

5-Amino-3-(2-trifluoromethylphenyl)isoquinolin-1-one hydrobromide (12g). Compound **31g** (22.4 mg, 70 μ mol) was stirred with HBr in AcOH (33%, 1.25 mL) at 65°C for 5 h. Evaporation yielded **12g** (25.2 mg, 94%) as a buff solid: mp >230°C; ^1H NMR (CD_3OD) δ 6.65 (1 H, s, 4-H), 7.69 (4 H, m, 7-H + Ph 4,5,6- H_3), 7.85 (1 H, d, $J = 8.5$ Hz, 6-H), 7.88 (1 H, d, $J = 8.0$ Hz, Ph 3-H), 8.45 (1 H, d, $J = 8.0$ Hz, 8-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 100.84 (4-C), 125.24 (q, $J = 271.3$ Hz, CF_3), 127.40 (q, $J = 5.3$ Hz, Ph 1-C), 127.56 (q, $J = 4.8$ Hz, Ph 3-C), 128.21 (7-C), 128.94 (6-C), 129.36 (8-C), 131.44 (Ph 6-C), 130.10 (q, $J = 30.6$ Hz, Ph 2-C), 132.95 (5-C), 133.23 (Ph 4-C), 133.50 (Ph 5-C), 141.90 (3-C), 163.54 (1-C); ^{19}F NMR (CD_3OD) δ -59.36 (s, CF_3); MS m/z 305.0872 ($\text{M} + \text{H}$) $^+$ ($\text{C}_{16}\text{H}_{12}\text{F}_3\text{N}_2\text{O}$ requires 305.0904).

5-Amino-3-(3-trifluoromethylphenyl)isoquinolin-1-one hydrobromide (12h). Compound **31h** (70.5 mg, 220 μ mol) was stirred with HBr in AcOH (33%, 3.75 mL) at 65°C for 7 h. Evaporation yielded **12h** (82.4 mg, 97%) as a buff solid: mp >230°C; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 7.05 (1 H, d, $J = 7.7$ Hz, 6-H), 7.16 (1 H, s, 4-H), 7.25 (1 H, t, $J = 7.8$ Hz, 7-H), 7.57 (1 H, d, $J = 7.7$ Hz, 8-H), 7.71 (1 H, t, $J = 7.8$ Hz, Ph 5-H), 7.77 (1 H, d, $J = 7.9$ Hz, Ph 4-H), 8.11 (1 H, d, $J = 8.0$ Hz, Ph 6-H), 8.17 (1 H, s, Ph 2-H), 11.56 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 99.07 (4-C), 116.52 (8-C), 119.27 (6-C), 123.26 (q, $J = 3.9$ Hz, Ph 2-C), 125.67 (q, $J = 3.9$ Hz, Ph 4-C), 126.19 (4a-C), 127.27 (7-C), 129.74 (q, $J = 31.8$ Hz, Ph 3-C), 129.89 (Ph 5-C), 130.52 (Ph 6-C), 134.85 (5-C), 136.28 (Ph 1-C), 137.31 (3-C), 162.53 (1-C); ^{19}F NMR ($(\text{CD}_3)_2\text{SO}$) δ -61.03 (s, CF_3); MS m/z 303.0740 ($\text{M} - \text{H}$) $^-$ ($\text{C}_{16}\text{H}_{10}\text{F}_3\text{N}_2\text{O}$ requires 303.0743).

5-Amino-3-(4-trifluoromethylphenyl)isoquinolin-1-one hydrobromide (12i). Compound **31i** (85 mg, 270 μ mol) was stirred with HBr in AcOH (33%, 4.0 mL) at 65°C for 7 h. Evaporation yielded **12i** (101 mg, 98%) as a buff solid: mp >230°C (lit.¹ mp 214–215°C for free base); ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 7.17 (2 H, m, 4,6- H_2), 7.32 (1 H, t, $J = 7.5$ Hz, 7-H), 7.67 (1 H, d, $J = 7.5$ Hz, 8-H), 7.88 (2 H, d, $J = 8.0$ Hz, Ph 3,5- H_2), 8.04 (2 H, d, $J = 8.0$ Hz, Ph 2,6- H_2), 11.63 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 99.53 (4-C), 117.08 (8-C), 118.87 (6-C), 124.11 (q, $J = 270.6$ Hz, CF_3), 125.64 (q, $J = 3.5$ Hz, Ph 3,5- C_2), 126.28 (4a-C), 127.41 (7-C + Ph 2,6- C_2), 129.20 (q, $J = 31.8$ Hz, Ph 4-C), 136.82 (Ph 1-C), 137.83 (3-C), 139.92 (5-C), 162.46 (1-C); ^{19}F NMR ($(\text{CD}_3)_2\text{SO}$) δ -61.02 (s, CF_3); MS m/z 303.0756 ($\text{M} - \text{H}$) $^-$ ($\text{C}_{16}\text{H}_{10}\text{F}_3\text{N}_2\text{O}$ requires 303.0743).

5-Amino-3-(4-fluorophenyl)isoquinolin-1-one hydrobromide (12j). Compound **31j** (65 mg, 24 μ mol) was stirred with HBr in AcOH (33%, 3.5 mL) at 65°C for 5 h. Evaporation

yielded **12j** (80 mg, 98%) as a buff solid: mp >230°C; ¹H NMR (CD₃OD) δ 6.99 (1 H, s, 4-H), 7.34 (3 H, m, 8-H & Ph 3,5-H₂), 7.39 (1 H, t, *J* = 8.5 Hz, 7-H), 7.45 (1 H, d, *J* = 8.5 Hz, 6-H), 7.89 (2 H, m, Ph 2,6-H₂), 11.71 (1 H, bs, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 98.62 (4-C), 115.48 (8-C), 115.68 (d, *J* = 6.1 Hz, Ph 3,5-C₂), 124.75 (Ph 1-C), 125.72 (3-C), 126.66 (7-C), 128.99 (d, *J* = 17.2 Hz, Ph 2,6-C₂), 130.11 (6-C), 137.96 (Ph 4-C), 141.34 (5-C), 162.63 (1-C); ¹⁹F NMR ((CD₃)₂SO) δ -112.47 (m, F); MS *m/z* 253.0756 (M – H)[–] (C₁₅H₁₀FN₂O requires 253.0777).

5-Amino-3-(2-chlorophenyl)isoquinolin-1-one hydrobromide (12k). Compound **31k** (40.4 mg, 140 μmol) was stirred with HBr in AcOH (33%, 1.6 mL) at 65°C for 5 h. Evaporation yielded **12k** (47.5 mg, 95%) as a buff solid: mp >230°C; ¹H NMR (CD₃OD) δ 6.71 (1 H, s, 4-H), 7.51 (2 H, m, Ph 4,5-H₂), 7.60 (2 H, m, Ph 3,6-H₂), 7.66 (1 H, t, *J* = 8.0 Hz, 7-H), 7.85 (1 H, d, *J* = 7.5 Hz, 6-H), 8.45 (1 H, d, *J* = 8.5 Hz, 8-H); ¹³C NMR (CD₃OD) (HSQC / HMBC) δ 100.92 (4-C), 127.61 (4a-C), 128.14 (7-C), 128.55 (Ph 5-C), 128.83 (6-C), 129.34 (8-C), 131.22 (Ph 3-C or Ph 6-C), 132.35 (Ph 6-C or Ph 3-C), 132.51 (Ph 4-C), 133.54 (5-C), 134.17 (Ph 2-C), 134.98 (Ph 1-C), 142.26 (3-C), 163.87 (1-C); MS *m/z* 273.0597 (M + H)⁺ (C₁₅H₁₂³⁷ClN₂O requires 273.0609), 271.0623 (M + H)⁺ (C₁₅H₁₂³⁵ClN₂O requires 271.0638).

5-Amino-3-(3-chlorophenyl)isoquinolin-1-one hydrobromide (12l). Compound **31l** (38.5 mg, 140 μmol) was stirred with HBr in AcOH (33%, 1.5 mL) at 65°C for 5 h. Evaporation yielded **12l** (46.1 mg, 97%) as a buff solid: mp >230°C; ¹H NMR (CD₃OD) δ 6.93 (1 H, s, 4-H), 7.55 (2 H, m, Ph 4,6-H₂), 7.63 (1 H, t, *J* = 7.5 Hz, 7-H), 7.71 (1 H, m, Ph 5-H), 7.79 (1 H, d, *J* = 7.5 Hz, 6-H), 7.83 (1 H, s, Ph 2-H), 8.41 (1 H, d, *J* = 8.0 Hz, 8-H); ¹³C NMR (CD₃OD) (HSQC / HMBC) δ 98.93 (4-C), 126.52 (Ph 5-C), 128.09 (7-C), 128.17 (Ph 2-C), 128.47 (6-C), 128.93 (8-C), 131.16 (Ph 4-C or Ph 6-C), 131.84 (Ph 6-C or Ph 4-C), 133.56 (5-C), 136.19 (Ph 1-C), 137.24 (Ph 3-C), 142.63 (3-C), 166.31 (1-C); MS *m/z* 273.0584 (M + H)⁺ (C₁₅H₁₂³⁷ClN₂O requires 273.0609), 271.0616 (M + H)⁺ (C₁₅H₁₂³⁵ClN₂O requires 271.0638).

5-Amino-3-(2,6-dichlorophenyl)isoquinolin-1-one hydrobromide (12n). Compound **31n** (12.7 mg, 40 μmol) was stirred with HBr in AcOH (33%, 1.0 mL) at 65°C for 5 h. Evaporation yielded **12n** (9.0 mg, 58%) as an amber solid: mp 226–228°C; ¹H NMR (CD₃OD) δ 6.73 (1 H, s, 4-H), 7.56 (1 H, t, *J* = 6.6 Hz, Ph 4-H), 7.63 (2 H, d, *J* = 7.0 Hz, Ph 3,5-H₂), 7.74 (1 H, t, *J* = 7.9 Hz, 7-H), 7.91 (1 H, d, *J* = 7.5 Hz, 6-H), 8.53 (1 H, d, *J* = 8.0 Hz, 8-H); ¹³C NMR (CD₃OD) (HSQC / HMBC) δ 101.69 (4-C), 128.44 (7-C), 128.98 (6-C), 129.47 (8-C), 129.57 (Ph 3,5-C₂), 133.13 (Ph 4-C), 133.42 (5-C), 133.88 (Ph 1-C), 136.46 (Ph 2,6-C₂), 139.26 (3-C), 164.19 (1-C); MS *m/z* 327.0065 (M + Na)⁺ (C₁₅H₁₀³⁵Cl₂N₂NaO requires 327.0068).

5-Amino-3-(4-hydroxyphenyl)isoquinolin-1-one hydrobromide (12p). Compound **31p** (55 mg, 210 μmol) was stirred with HBr in AcOH (33%, 2.5 mL) at 65°C for 16 h. Evaporation yielded **12p** (68.5 mg, 98%) as a buff solid: mp >230°C; ¹H NMR ((CD₃)₂SO) δ 6.88 (3 H, m, 4-H + Ph 3,5-H₂), 7.36 (2 H, m, 6,7-H₂), 7.67 (2 H, d, *J* = 9.0 Hz, Ph 2,6-H₂), 7.88 (1 H, d, *J* = 9.0 Hz, 8-H), 11.46 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 96.01 (4-C), 115.55 (Ph 3,5-C₂), 124.59 (7-C), 125.36 (6-C), 125.94 (8-C), 128.09 (Ph 2,6-C₂), 139.99 (3-C), 158.69 (Ph 4-C), 162.45 (1-C); MS *m/z* 253.0958 (M + H)⁺ (C₁₅H₁₃N₂O₂ requires 253.0977).

5-Amino-3-(2-phenylethyl)isoquinolin-1-one hydrobromide (12s). Compound **39** (40 mg, 140 μmol) was stirred with HBr in AcOH (33%, 2.0 mL) at 65°C for 16 h. Evaporation yielded **12s** (35 mg, 70%) as a red-brown solid: mp >230°C; ¹H NMR (CD₃OD) δ 2.95 (2 H, t, *J* = 7.0 Hz, ethyl 1-H₂), 3.06 (2 H, t, *J* = 6.0 Hz, ethyl 2-H₂), 6.48 (1 H, s, 4-H), 7.24 (5 H,

m, Ph-H₅), 7.56 (1 H, t, J = 8.0 Hz, 7-H), 7.75 (1 H, dd, J = 8.0, 1.0 Hz, 6-H), 8.38 (1 H, d, J = 8.0 Hz, 8-H); ¹³C NMR (CD₃OD) (HSQC / HMBC) δ 35.83 (ethyl 2-C), 36.51 (ethyl 1-C), 97.82 (4-C), 126.76 (7-C), 127.07 (Ph 3-C), 127.48 (6-C), 129.36 (8-C), 129.43 (Ph 2,6-C₂), 129.62 (Ph 3,5-C₂), 134.04 (5-C), 141.57 (Ph 1-C), 145.88 (3-C), 164.03 (1-C); MS m/z 265.1320 (M + H)⁺ (C₁₇H₁₇N₂O requires 265.1341).

5-Amino-3-(4-aminocarbonylphenyl)isoquinolin-1-one hydrobromide (12u). Compound **31r** (14 mg, 50 μ mol) was stirred with HBr in AcOH (33%, 1.0 mL) at 65°C for 16 h. Evaporation yielded **12u** (17.0 mg, 98%) as an amber solid: mp >230°C; ¹H NMR ((CD₃)₂SO) δ 4.4 (3 H, m, ⁺NH₃), 7.14 (1 H, d, J = 7.8 Hz, 6-H), 7.17 (1 H, s, 4-H), 7.30 (1 H, t, J = 7.8 Hz, 7-H), 7.46 (1 H, br, CONHH), 7.66 (1 H, d, J = 7.7 Hz, 8-H), 7.92 (2 H, d, J = 8.5 Hz, Ph 2,6-H₂), 7.99 (2 H, d, J = 8.5 Hz, Ph 3,5-H₂), 8.08 (1 H, br, CONHH), 11.55 (1 H, bs, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 98.81 (4-C), 119.83 (8-C), 120.91 (6-C), 126.12 (Ph 4-C), 126.30 (Ph 2,6-C₂), 127.09 (7-C), 127.89 (Ph 3,5-C₂), 134.48 (3-C), 136.30 (Ph 1-C), 138.15 (5-C), 162.50 (1-C), 167.13 (CONH₂); MS m/z 278.0947 (M - H)⁻ (C₁₆H₁₂N₃O₂ requires 278.0930).

3-(4-(1,1-Dimethylethyl)phenyl)-5-methylisoquinolin-1-one (13c). BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol) was added to dry Pr₂NH (127.5 mg, 1.3 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-(1,1-Dimethylethyl)benzonitrile (180 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and washing (EtOH) gave **13c** (96.5 mg, 29%) as a white solid: mp 204-206°C; IR ν_{\max} 3295, 1642 cm⁻¹; ¹H NMR ((CD₃)₂SO) (COSY) δ 1.33 (9 H, s, CMe₃), 2.55 (3 H, s, 5-Me), 6.82 (1 H, s, 4-H), 7.35 (1 H, t, J = 7.6 Hz, 7-H), 7.51 (2 H, d, J = 7.6 Hz, Ph 3,5-H₂), 7.54 (1 H, d, J = 7.2 Hz, 6-H), 7.75 (2 H, d, J = 7.6 Hz, Ph 2,6-H₂), 8.06 (1 H, d, J = 8.0 Hz, 8-H), 11.48 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.75 (Me), 30.97 (CMe₃), 34.44 (CMe₃), 99.60 (4-C), 124.56 (8-C), 124.86 (8a-C), 125.51 (Ph 3,5-C₂), 125.72 (7-C), 126.56 (Ph 2,6-C₂), 131.44 (Ph 1-C), 133.15 (6-C), 133.60 (4a-C), 136.69 (5-C), 139.84 (3-C), 151.87 (Ph 4-C), 162.97 (1-C); MS m/z 292.1686 (M + H)⁺ (C₂₀H₂₂NO requires 292.1703).

3-(4-Methoxyphenyl)-5-methylisoquinolin-1-one (13d). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr₂NH (141 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Methoxybenzonitrile (151 mg, 1.1 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and washing (EtOH) gave **13d** (48 mg, 17%) as a white solid: mp 207-208°C; ¹H NMR ((CD₃)₂SO) (COSY) δ 2.54 (1 H, s, 5-Me), 3.82 (3 H, s, OMe), 6.77 (1 H, s, 4-H), 7.04 (2 H, d, J = 8.8 Hz, Ph 3,5-H₂), 7.33 (1 H, t, J = 7.6 Hz, 7-H), 7.53 (1 H, d, J = 7.1 Hz, 6-H), 7.78 (2 H, d, J = 8.8 Hz, Ph 2,6-H₂), 8.05 (1 H, d, J = 8.0 Hz, 8-H), 11.45 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.81 (5-Me), 55.34 (OMe), 98.87 (4-C), 114.15 (Ph 3,5-C₂), 124.57 (8-C), 124.63 (8a-C), 125.51 (7-C), 126.51 (Ph 1-C), 128.23 (Ph 2,6-C₂), 133.15 (6-C), 133.49 (4a-C), 136.86 (5-C), 139.70 (3-C), 160.14 (Ph 4-C), 163.02 (1-C); MS m/z 553.2099 (2 M + Na)⁺ (C₃₄H₃₀N₂NaO₄ requires 553.2104); 288.0994 (M + Na)⁺ (C₁₇H₁₅NNaO₂ requires 288.1000), 266.1179 (M + H)⁺ (C₁₇H₁₆NO₂ requires 266.1181).

5-Methyl-3-(4-trifluoromethylphenyl)isoquinolin-1-one (13e). BuLi (1.6 M in hexanes, 1.1 mL, 1.7 mmol) was added to dry Pr^i_2NH (202 mg, 2.0 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (300 mg, 1.7 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 4-Trifluoromethylbenzonitrile (289 mg, 1.7 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was extracted with CH_2Cl_2 . The extract was washed thrice with brine and dried. Evaporation and recrystallisation (EtOH) (25 mL) gave **13e** (242 mg, 47%) as white crystals: mp $251\text{--}252^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) (COSY) δ 2.56 (3 H, s, Me), 6.96 (1 H, s, 4-H), 7.40 (1 H, t, $J = 7.6$ Hz, 7-H), 7.57 (1 H, d, $J = 7.2$ Hz, 6-H), 7.84 (2 H, d, $J = 8.3$ Hz, Ph 3,5- H_2), 8.03 (2 H, d, $J = 8.2$ Hz, Ph 2,6- H_2), 8.08 (1 H, d, $J = 8.0$ Hz, 8-H), 11.75 (1 H, br, N-H); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 18.77 (Me), 101.54 (4-C), 124.62 (8-C), 125.23 (q, $J = 295.9$ Hz, CF_3), 125.51 (8a-C), 125.56 (q, $J = 3.6$ Hz, Ph 3,5- C_2), 126.54 (7-C), 129.25 (q, $J = 31.6$ Hz, Ph 4-C), 133.40 (6-C), 134.21 (4a-C), 136.29 (5-C), 138.10 (Ph 1-C), 138.36 (3-C), 162.91 (1-C); ^{19}F NMR ($(\text{CD}_3)_2\text{SO}$) δ -61.08 (s, CF_3); MS m/z 302.0808 (M - H) $^-$ ($\text{C}_{17}\text{H}_{11}\text{F}_3\text{NO}$ requires 308.0798).

3-(2-Chlorophenyl)-5-methylisoquinolin-1-one (13f). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr^i_2NH (141 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 2-Chlorobenzonitrile (155 mg, 1.1 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 . This mixture was washed thrice with brine and dried. The evaporation residue was washed (EtOH) to give **13f** (4.9 mg, 2%) as a white solid: mp $178\text{--}180^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) (COSY) δ 2.53 (3 H, s, Me), 6.58 (1 H, s, 4-H), 7.41 (1 H, t, $J = 7.7$ Hz, 7-H), 7.47 (1 H, td, $J = 7.5, 1.3$ Hz, Ph 4-H), 7.51 (1 H, td, $J = 7.5, 2.0$ Hz, Ph 5-H), 7.59 (3 H, m, 6-H + Ph 3,6- H_2), 8.08 (1 H, d, $J = 8.0$ Hz, 8-H), 11.59 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 18.69 (Me), 102.43 (4-C), 124.61 (8-C), 125.33 (8a-C), 126.25 (7-C), 127.34 (Ph 4-C), 129.70 (Ph 6-C), 130.84 (Ph 5-C), 131.56 (Ph 3-C), 132.29 (Ph 2-C), 133.22 (6-C), 133.69 (4a-C), 134.24 (Ph 1-C), 136.31 (5-C), 138.15 (3-C), 162.24 (1-C); MS m/z 292.0514 (M + Na) $^+$ ($\text{C}_{16}\text{H}_{12}^{35}\text{ClNNaO}$ requires 292.0505).

3-(3-Chlorophenyl)-5-methylisoquinolin-1-one (13g). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr^i_2NH (141 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **42** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 3-Chlorobenzonitrile (155 mg, 1.1 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 , washed thrice with brine and dried. Evaporation and recrystallisation (EtOH) gave **13g** (33 mg, 11%) as a white solid: mp $275\text{--}276^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) (COSY) δ 2.57 (3 H, s, Me), 6.93 (1 H, s, 4-H), 7.39 (1 H, t, $J = 7.6$ Hz, 7-H), 7.52 (2 H, m, Ph 4,5- H_2), 7.57 (1 H, d, $J = 7.2$ Hz, 6-H), 7.80 (1 H, m, Ph 6-H), 7.93 (1 H, s, Ph 2-H), 8.07 (1 H, d, $J = 8.0$ Hz, 8-H), 11.61 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 18.82 (Me), 100.92 (4-C), 124.57 (8-C), 125.28 (8a-C), 125.64 (Ph 6-C), 126.32 (7-C), 126.74 (Ph 2-C), 129.01 (Ph 4-C), 130.54 (Ph 5-C), 133.33 (6-C), 133.55 (Ph 1-C), 134.14 (4a-C), 136.20 (Ph 3-C), 136.41 (5-C), 138.31 (3-C), 162.87 (1-C); MS m/z 292.0453 (M + Na) $^+$ ($\text{C}_{16}\text{H}_{12}^{35}\text{ClNNaO}$ requires 292.0506), 270.0661 (M + H) $^+$ ($\text{C}_{16}\text{H}_{13}^{35}\text{ClNO}$ requires 270.0686).

3-(4-Chlorophenyl)-5-methylisoquinolin-1-one (13h). BuLi (1.6 M in hexanes, 1.1 mL, 1.7 mmol) was added to dry Pr^i_2NH (202 mg, 2.0 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (300 mg, 1.7 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 4-Chlorobenzonitrile (233 mg, 1.7 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 2 h. Water (1.0 mL) was added, followed by CH_2Cl_2 (20 mL). The precipitate was collected by filtration to give **13h** (456 mg, 99%) as a white solid: mp $>360^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) (COSY) δ 2.61 (3 H, s, Me), 6.93 (1 H, s, 4-H), 7.44 (1 H, t, $J = 7.6$ Hz, 7-H), 7.61 (3 H, d, $J = 8.5$ Hz, 6-H + Ph 2,6- H_3), 7.90 (2 H, d, $J = 8.6$ Hz, Ph 3,5- H_2), 8.12 (1 H, d, $J = 7.8$ Hz, 8-H), 11.70 (1 H, s, N-H); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 18.80 (Me), 100.49 (4-C), 124.60 (8-C), 125.11 (8a-C), 126.19 (7-C), 128.73 (Ph 2,6- C_2), 128.78 (Ph 3,5- C_2), 133.01 (4a-C), 133.34 (6-C), 133.96 (Ph 1,4- C_2), 136.49 (5-C), 138.67 (3-C), 162.95 (1-C); MS m/z 270 ($\text{M} - \text{H}$) $^-$, 268.0533 ($\text{M} - \text{H}$) $^-$ ($\text{C}_{16}\text{H}_{11}^{35}\text{ClNO}$ requires 268.0535).

3-(2,6-Dichlorophenyl)-5-methylisoquinolin-1-one (13i). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr^i_2NH (141 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 2,6-Dichlorobenzonitrile (194 mg, 1.1 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 , washed thrice with brine and dried. Evaporation and recrystallisation (EtOH) gave **13i** (35 mg, 10%) as a pale buff solid: mp $202\text{--}204^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) (COSY) δ 2.47 (3 H, s, Me), 6.58 (1 H, s, 4-H), 7.43 (1 H, t, $J = 7.6$ Hz, 7-H), 7.55 (1 H, t, $J = 7.2$ Hz, Ph 4-H), 7.58 (1 H, d, $J = 7.3$ Hz, 6-H), 7.59 (2 H, d, $J = 7.6$ Hz, Ph 3,5- H_2), 8.09 (1 H, d, $J = 7.9$ Hz, 8-H), 11.62 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 18.66 (Me), 102.81 (4-C), 124.61 (8-C), 125.58 (8a-C), 126.45 (7-C), 128.28 (Ph 3,5- C_2), 131.67 (Ph 4-C), 133.19 (Ph 1-C), 133.29 (6-C), 133.75 (4a-C), 134.69 (Ph 2,6- C_2), 135.20 (3-C), 136.24 (5-C), 162.37 (1-C); MS m/z 326.0991 ($\text{M} + \text{Na}$) $^+$ ($\text{C}_{16}\text{H}_{11}^{35}\text{Cl}_2\text{NNO}$ requires 326.0115), 304.0286 ($(\text{M} + \text{H})^+$) ($\text{C}_{16}\text{H}_{12}^{35}\text{Cl}_2\text{NO}$ requires 304.0296).

3-(4-Bromophenyl)-5-methylisoquinolin-1-one (13j). BuLi (1.6 M in hexanes, 0.9 mL, 1.4 mmol) was added to dry Pr^i_2NH (162 mg, 1.6 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (241 mg, 1.4 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 4-Bromobenzonitrile (248 mg, 1.4 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 (20 mL). The solid was collected by filtration and washed (EtOH) to give **13j** (181 mg, 42%) as a white solid: mp $278\text{--}279^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) (COSY) δ 2.55 (3 H, s, Me), 6.88 (1 H, s, 4-H), 7.38 (1 H, t, $J = 7.7$ Hz, 7-H), 7.56 (1 H, d, $J = 7.2$ Hz, 6-H), 7.69 (2 H, d, $J = 8.5$ Hz, Ph 2,6- H_2), 7.78 (2 H, d, $J = 8.5$ Hz, Ph 3,5- H_2), 8.07 (1 H, d, $J = 8.0$ Hz, 8-H), 11.59 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 18.81 (Me), 100.47 (4-C), 122.66 (Ph 4-C), 124.62 (8-C), 125.13 (8a-C), 126.20 (7-C), 129.03 (Ph 3,5- C_2), 131.66 (Ph 2,6- C_2), 133.34 (6-C), 133.43 (Ph 1-C), 133.97 (4a-C), 136.51 (5-C), 138.81 (3-C), 162.99 (1-C); MS m/z 335.9966 ($\text{M} + \text{Na}$) $^+$ ($\text{C}_{16}\text{H}_{12}^{79}\text{BrNNO}$ requires 336.0000).

5-Methyl-3-(4-phenylethynylphenyl)isoquinolin-1-one (13k). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr^i_2NH (141 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at this temperature for 10 min. Compound **41** (230 mg, 1.1 mmol)

in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. Compound **43** (194 mg, 1.1 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂. The solid was collected by filtration and washed (EtOH) to give **13k** (117 mg, 31%) as a white solid: mp 285-287°C; ¹H NMR ((CD₃)₂SO) (COSY) δ (2.57, s, Me), 6.94 (1 H, s, 4-H), 7.39 (1 H, t, *J* = 7.6 Hz, 7-H), 7.45 (3 H, m, Ph 3,4,5-H₃), 7.56 (1 H, d, *J* = 7.4 Hz, 6-H), 7.59 (2 H, m, Ph 2,6-H₂), 7.67 (2 H, d, *J* = 8.0 Hz, Ar 3,5-H₂), 7.90 (2 H, d, *J* = 8.0 Hz, Ar 2,6-H₂), 8.08 (1 H, d, *J* = 7.9 Hz, 8-H), 11.62 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.82 (Me), 88.99 (ethyne 1-C), 90.86 (ethyne 2-C), 100.64 (4-C), 122.09 (Ph 1-C), 122.92 (Ar 4-C), 124.61 (8-C), 125.18 (8a-C), 126.21 (7-C), 126.15 (Ar 2,6-C₂), 128.84 (Ph 3,5-C₂), 129.03 (Ph 10-C), 131.47 (Ph 2,6-C₂), 131.66 (Ar 3,5-C₂), 133.29 (6-C), 134.03 (4a-C), 134.17 (Ar 1-C), 136.50 (5-C), 139.00 (3-C), 163.00 (1-C); MS *m/z* 358.1218 (M + Na)⁺ (C₂₄H₁₇NNaO requires 358.1208), 336.1402 (M + H)⁺ (C₂₄H₁₈NO requires 336.1388).

5-Methyl-3-(4-(piperidin-1-ylmethyl)phenyl)isoquinolin-1-one (13m). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr^{*i*}₂NH (142 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. Compound **45b** (226 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at this temperature, then at room temperature for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with saturated brine and dried. Evaporation and washing (EtOH) gave **13m** (78 mg, 21%) as a white solid: mp 196-197°C; IR *v*_{max} 3440 (NH), 1644 (C=O); ¹H NMR ((CD₃)₂SO) δ 1.40 (2 H, m, piperidine 4-H₂), 1.50 (4 H, m, piperidine 3,5-H₄), 2.34 (4 H, m, piperidine 2,6-H₄), 2.55 (3 H, s, Me), 3.47 (2 H, s, PhCH₂), 6.84 (1 H, s, 4-H), 7.36 (1 H, t, *J* = 7.7 Hz, 7-H), 7.40 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H₂), 7.54 (1 H, d, *J* = 7.1 Hz, 6-H), 7.76 (2 H, d, *J* = 8.2 Hz, Ph 2,6-H₂), 8.06 (1 H, d, *J* = 7.9 Hz, 8-H), 11.48 (1 H, bs, N-H); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.76 (Me), 23.96 (piperidine 4), 25.55 (piperidine 3,5-C₂), 53.91 (piperidine 2,6-C₂), 62.37 (PhCH₂), 99.73 (4-C), 124.56 (8-C), 124.90 (8a-C), 125.79 (7-C), 126.61 (Ph 2,6-C₂), 129.01 (Ph 3,5-C₂), 132.67 (Ph 1-C), 133.18 (6-C), 133.68 (4a-C), 136.66 (5-C), 139.78 (Ph 4-C), 140.06 (3-C), 162.95 (1-C); MS *m/z* 665.3884 (2 M + H)⁺ (C₄₄H₄₉N₄O₂ requires 665.3855), 355.1805 (M + Na)⁺ (C₂₂H₂₄N₂NaO requires 355.1786).

5-Methyl-3-(4-(pyrrolidin-1-ylmethyl)phenyl)isoquinolin-1-one hydrochloride (13n). BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol) was added to dry Pr^{*i*}₂NH (127.5 mg, 1.3 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.13 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. Compound **45c** (210.5 mg, 1.13 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and washing (EtOH) gave **13n** (32 mg, 9%) as a pale yellow solid: mp >360°C; IR *v*_{max} 3413, 1640 cm⁻¹; The solid was then treated for 16 h with aq. HCl (6.0 M, 2.0 mL). Evaporation and drying gave the HCl salt as a white solid: mp >360°C; ¹H NMR ((CD₃)₂SO) δ 1.70 (4 H, m, pyrrolidine 3,4-H₄), 2.44 (4 H, m, pyrrolidine 2,5-H₄), 2.54 (3 H, s, Me), 3.61 (2 H, s, PhCH₂), 6.83 (1 H, s, 4-H), 7.35 (1 H, t, *J* = 7.7 Hz, 7-H), 7.41 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H₂), 7.54 (1 H, d, *J* = 7.2 Hz, 6-H), 7.76 (2 H, d, *J* = 8.2 Hz, Ph 2,6-H₂), 8.05 (1 H, d, *J* = 7.9 Hz, 8-H), 11.52 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.77 (Me), 23.12 (pyrrolidine 3,4-C₂), 53.50 (pyrrolidine 2,5-C₂), 59.15 (PhCH₂), 99.72 (4-C), 124.55 (8-C), 124.92 (8a-C), 125.80 (7-C), 126.64 (Ph 2,6-C₂), 128.71 (Ph 3,5-C₂), 132.64 (Ph 1-C),

133.30 (6-C), 133.68 (4a-C), 136.81 (5-C), 139.86 (3-C), 140.96 (Ph 4-C), 163.24 (1-C); MS m/z 319.1788 ($M + H$)⁺ ($C_{21}H_{23}N_2O$ requires 319.1810).

5-Methyl-3-((4-methylpiperazin-1-yl)methyl)phenylisoquinolin-1-one dihydrochloride (13o). BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol) was added to dry Prⁱ₂NH (128 mg, 1.3 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.13 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. Compound **45d** (243 mg, 1.13 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. The evaporation residue was washed (EtOH) to give **13o** (8 mg, 2%) as a white solid: mp >360°C. The solid was treated for 16 h with aq. HCl (6 M, 1.0 mL). Evaporation and drying gave the 2.HCl salt: mp >360°C; IR ν_{\max} 3419, 1636 cm⁻¹; ¹H NMR ((CD₃)₂SO) δ 2.14 (3 H, s, NMe), 2.35 (8 H, m, piperazine-H₈), 2.54 (3 H, s, 5-Me), 3.49 (PhCH₂), 6.83 (1 H, s, 4-H), 7.35 (1 H, t, $J = 7.7$ Hz, 7-H), 7.39 (2 H, d, $J = 8.2$ Hz, Ph 3,5-H₂), 7.54 (1 H, d, $J = 7.2$ Hz, 6-H), 7.76 (2 H, d, $J = 8.2$ Hz, Ph 2,6-H₂), 8.05 (1 H, d, $J = 7.9$ Hz, 8-H), 11.51 (1 H, br, N-H); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.76 (5-Me), 40.08 (NMe), 52.57 (piperazine 2,6-C₂), 54.70 (piperazine 3,5-C₂), 61.57 (PhCH₂), 99.75 (4-C), 124.56 (8-C), 124.92 (8a-C), 125.81 (7-C), 126.65 (Ph 2,6-C₂), 129.65 (Ph 3,5-C₂), 132.79 (Ph 1-C), 133.18 (6-C), 133.69 (4a-C), 136.65 (5-C), 139.67 (Ph 4-C), 139.75 (3-C), 162.94 (1-C); MS m/z 348.2076 ($M + H$)⁺ ($C_{22}H_{26}N_3O$ requires 348.2076).

5-Methyl-3-(pyridin-4-yl)isoquinolin-1-one (13p). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Prⁱ₂NH (142 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Cyanopyridine (118 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and recrystallisation (EtOH) gave **13p** (16.5 mg, 6%) as white crystals: mp 268-269°C; IR ν_{\max} 3450, 1654 cm⁻¹; ¹H NMR ((CD₃)₂SO) (COSY) δ 2.59 (3 H, s, Me), 7.11 (1 H, s, 4-H), 7.44 (1 H, t, $J = 7.7$ Hz, 7-H), 7.60 (1 H, d, $J = 7.2$ Hz, 6-H), 7.87 (2 H, d, $J = 6.2$ Hz, Ph 3,5-H₂), 8.10 (1 H, d, $J = 8.0$ Hz, 8-H), 8.69 (2 H, d, $J = 6.2$ Hz, Ph 2,6-H₂), 11.70 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.76 (Me), 101.87 (4-C), 120.96 (pyridine 3,5-C₂), 124.65 (8-C), 125.83 (8a-C), 126.91 (7-C), 133.49 (6-C), 134.50 (4a-C), 136.06 (5-C), 137.06 (pyridine 4-C), 141.03 (3-C), 150.13 (pyridine 2,6-C₂), 162.85 (1-C); MS m/z 235.0864 ($M - H$)⁻ ($C_{15}H_{11}N_2O$ requires 235.0871).

3-(Benzo-1,3-dioxol-5-yl)-5-methylisoquinolin-1-one (13q). BuLi (1.6 M in hexanes, 0.70 mL, 1.1 mmol) was added to dry Prⁱ₂NH (141 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 5-Cyanobenzo-1,3-dioxole (166 mg, 1.1 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂. The solid was collected by filtration, washed (EtOH) and dried to give **13q** (199 mg, 63%) as a white solid. mp >360°C; ¹H NMR ((CD₃)₂SO) (COSY) δ 2.54 (3 H, s, Me), 6.10 (2 H, s, CH₂), 6.78 (1 H, s, 4-H), 7.02 (1 H, d, $J = 8.2$ Hz, benzodioxole 6-H), 7.33 (1 H, t, $J = 7.7$ Hz, 7-H), 7.34 (1 H, dd, $J = 8.1, 1.8$ Hz, benzodioxole 7-H), 7.43 (1 H, d, $J = 1.8$ Hz, benzodioxole 4-H), 7.52 (1 H, d, $J = 7.2$ Hz, 6-H), 8.04 (1 H, d, $J = 8.0$ Hz, 8-H), 11.44 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 18.83 (Me), 99.37 (4-C), 101.52 (CH₂), 107.27 (benzodioxole 4-C), 108.46 (benzodioxole 7-C), 121.07 (benzodioxole

6-C), 124.56 (8-C), 124.72 (8a-C), 125.60 (7-C), 128.40 (benzodioxole 5-C), 133.12 (6-C), 133.62 (4a-C), 136.80 (5-C), 139.77 (3-C), 147.71 (benzodioxole 7a-C), 148.17 (benzodioxole 3a-C), 163.14 (1-C); MS m/z 278.0797 ($M - H$)⁻ ($C_{17}H_{12}NO_3$ requires 278.0817).

5-Methyl-3-(thiophen-3-yl)isoquinolin-1-one (13r). BuLi (2.5 M in hexanes, 0.46 mL, 1.1 mmol) was added to dry Pr^i_2NH (127.5 mg, 1.3 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **41** (200 mg, 1.13 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 3-Cyanothiophene (123 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 and washed thrice with saturated brine. Drying, evaporation and washing (EtOH) gave **13r** (17 mg, 6%) as a pale buff solid: mp >360°C; IR ν_{max} 3448, 1647 cm^{-1} ; 1H NMR ($(CD_3)_2SO$) (COSY) δ 2.56 (3 H, s, Me), 6.99 (1 H, s, 4-H), 7.34 (1 H, t, $J = 7.6$ Hz, 7-H), 7.54 (1 H, d, $J = 7.1$ Hz, 6-H), 7.70 (1 H, m, thiophene 4-H), 7.78 (1 H, d, $J = 4.6$ Hz, thiophene 5-H), 8.04 (1 H, d, $J = 8.0$ Hz, 8-H), 8.28 (1 H, d, $J = 1.5$ Hz, thiophene 2-H), 11.47 (1 H, br, NH); ^{13}C NMR ($(CD_3)_2SO$) (HSQC / HMBC) δ 18.80 (Me), 99.09 (4-C), 123.46 (thiophene 2-C), 124.58 (8-C), 124.95 (8a-C), 125.74 (7-C), 126.16 (thiophene 5-C), 127.27 (thiophene 4-C), 133.25 (6-C), 133.73 (4a-C), 134.95 (thiophene 1-C), 135.37 (3-C), 136.72 (5-C), 162.80 (1-C); MS m/z 264.0454 ($M + Na$)⁺ ($C_{14}H_{11}NNaOS$ requires 264.0459).

5-Fluoro-3-(4-methylphenyl)isoquinolin-1-one (14b). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr^i_2NH (142 mg, 1.4 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **49** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Methylbenzonitrile (129 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 , washed thrice with brine and dried. Evaporation and recrystallisation (EtOH) gave **14b** (50 mg, 18%) as white crystals: mp 232-233°C; IR ν_{max} 3481, 1668, 1235 cm^{-1} ; 1H NMR ($(CD_3)_2SO$) (COSY) δ 2.37 (3 H, s, Me), 6.81 (1 H, s, 4-H), 7.30 (2 H, d, $J = 8.0$ Hz, Ph 3,5- H_2), 7.48 (1 H, m, 7-H), 7.58 (1 H, t, $J = 8.1$ Hz, 6-H), 7.71 (2 H, d, $J = 8.0$ Hz, Ph 2,6- H_2), 8.03 (1 H, d, $J = 8.0$ Hz, 8-H), 11.70 (1 H, br, NH); ^{13}C NMR ($(CD_3)_2SO$) (HSQC / HMBC) δ 20.83 (Me), 94.19 (d, $J = 5.1$ Hz, 4-C), 117.57 (d, $J = 19.5$ Hz, 6-C), 122.77 (d, $J = 3.3$ Hz, 8-C), 126.46 (d, $J = 3.4$ Hz, 8a-C), 126.59 (d, $J = 7.6$ Hz, 7-C), 126.79 (Ph 2,6- C_2), 127.06 (d, $J = 16.5$ Hz, 4a-C), 129.40 (Ph 3,5- H_2), 130.74 (Ph 1-C), 139.38 (Ph 4-C), 141.40 (3-C), 157.26 (d, $J = 248.1$ Hz, 5-C), 161.81 (d, $J = 2.8$ Hz, 1-C); ^{19}F NMR ($(CD_3)_2SO$) δ -122.08 (dd, $J = 10.4$, 5.2 Hz, F); MS m/z 252.0807 ($M - H$)⁻ ($C_{16}H_{11}FNO$ requires 252.0824).

5-Fluoro-3-(4-methoxyphenyl)isoquinolin-1-one (14c). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr^i_2NH (131 mg, 1.3 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **49** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Methoxybenzonitrile (147 mg, 1.1 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 , washed thrice with brine and dried. Evaporation and washing (EtOH) gave **14c** (8.1 mg, 3%) as an off-white solid: mp 238-240°C; 1H NMR ($(CD_3)_2SO$) δ 3.82 (3 H, s, Me), 6.78 (1 H, s, 4-H), 7.05 (2 H, d, $J = 8.9$ Hz, Ph 3,5- H_2), 7.45 (1 H, m, 7-H), 7.57 (1 H, t, $J = 8.9$ Hz, 6-H), 7.77 (2 H, d, $J = 8.9$ Hz, Ph 2,6- H_2), 8.02 (1 H, d, $J = 8.0$ Hz, 8-H), 11.66 (1 H, br, NH); ^{13}C NMR ($(CD_3)_2SO$) (HSQC / HMBC) δ 55.37 (Me), 93.59 (d, $J = 5.3$ Hz, 4-C), 114.23 (Ph 3,5- C_2), 117.52 (d, $J = 19.6$ Hz, 6-C), 122.74 (d, $J = 3.2$ Hz, 8-C), 125.84 (Ph 1-

C), 126.24 (d, $J = 3.6$ Hz, 8a-C), 126.32 (d, $J = 7.6$ Hz, 7-C), 129.20 (d, $J = 16.5$ Hz, 4a-C), 128.35 (Ph 2,6-C₂), 141.19 (3-C), 157.19 (d, $J = 247.5$ Hz, 5-C), 160.41 (Ph 4-C), 161.82 (1-C); ¹⁹F NMR ((CD₃)₂SO) δ -122.20 (dd, $J = 9.9, 5.2$ Hz, F); MS m/z 561.1593 (2 M + Na)⁺ (C₃₂H₂₄F₂N₂NaO₄ requires 561.1602), 292.0747 (M + Na)⁺ (C₁₆H₁₂FNNaO₂ requires 292.0750).

5-Fluoro-3-(4-trifluoromethylphenyl)isoquinolin-1-one (14d). BuLi (1.6 M in hexanes, 0.9 mL, 1.4 mmol) was added to dry Pr₂NH (170 mg, 1.7 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **49** (250 mg, 1.4 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Trifluoromethylbenzonitrile (236 mg, 1.4 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂ (20 mL). The solid was collected by filtration and washed (EtOH) to give **14d** (424 mg, 99%) as a white solid: mp >360°C; ¹H NMR ((CD₃)₂SO) (COSY) δ 6.97 (1 H, s, 4-H), 7.55 (1 H, td, $J = 7.6, 5.7$ Hz, 7-H), 7.63 (1 H, t, $J = 8.7$ Hz, 6-H), 7.86 (2 H, d, $J = 8.1$ Hz, Ph 3,5-H₂), 8.05 (3 H, m, Ph 2,6-H₂ + 8-H), 11.92 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 96.30 (d, $J = 4.9$ Hz, 4-C), 117.86 (d, $J = 19.5$ Hz, 6-C), 122.83 (d, $J = 3.4$ Hz, 8-C), 124.07 (q, $J = 270.1$ Hz, CF₃), 125.63 (q, $J = 3.5$ Hz, Ph 3,5-H₂), 126.59 (d, $J = 16.3$ Hz, 4a-C), 126.91 (8a-C), 127.52 (d, $J = 7.6$ Hz, 7-C), 127.99 (Ph 2,6-C₂), 129.58 (q, $J = 31.9$ Hz, Ph 4-C), 137.47 (1-C), 139.86 (3-C), 157.44 (d, $J = 248.5$ Hz, 5-C), 161.70 (1-C); ¹⁹F NMR (DMSO) δ -61.19 (3 F, s, CF₃), -121.55 (1 F, m, F); MS m/z 306.0559 (M - H)⁻ (C₁₆H₈F₄NO requires 306.0548)

3-(4-Chlorophenyl)-5-fluoroisoquinolin-1-one (14f). BuLi (1.6 M in hexanes, 0.9 mL, 1.4 mmol) was added to dry Pr₂NH (170 mg, 1.7 mmol) in dry tetrahydrofuran (2.0 mL) at -78°C and the mixture was stirred at this temperature for 10 min. Compound **49** (250 mg, 1.4 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Chlorobenzonitrile (190 mg, 1.4 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂ (20 mL). The solid was collected by filtration and washed (EtOH) to give **14f** (269 mg, 71%) as a white solid: mp 296-297°C; ¹H NMR ((CD₃)₂SO) (COSY) δ 6.86 (1 H, s, 4-H), 7.49 (1 H, m, 7-H), 7.57 (3 H, m, 6-H + Ph 3,5-H₂), 7.84 (2 H, d, $J = 8.6$ Hz, Ph 2,6-H₂), 8.05 (1 H, d, $J = 7.9$ Hz, 8-H), 11.63 (1 H, br, N-H); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 94.91 (d, $J = 5.4$ Hz, 4-C), 117.36 (d, $J = 19.6$ Hz, 6-C), 122.53 (d, $J = 3.5$ Hz, 8-C), 126.73 (d, $J = 8.0$ Hz, 7-C), 126.52 (8a-C), 126.65 (d, $J = 16.2$ Hz, 4a-C), 128.51 (Ph 3,5-C₂), 128.57 (Ph 2,6-C₂), 132.26 (Ph 1-C), 134.15 (Ph 4-C), 140.00 (3-C), 157.15 (d, $J = 248.4$ Hz, 5-C), 161.42 (1-C); ¹⁹F NMR ((CD₃)₂SO) δ -122.79 (m, F); MS m/z 272.0762 (M - H)⁻ (C₁₅H₈³⁵ClFNO requires 272.0784).

3-(4-Bromophenyl)-5-fluoroisoquinolin-1-one (14g). BuLi (1.6 M in hexanes, 0.64 mL, 1.2 mmol) was added to dry Pr₂NH (121 mg, 1.2 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **49** (180 mg, 1.0 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Bromobenzonitrile (186 mg, 1.0 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂ (20 mL). The solid was collected by filtration and washed (EtOH) to give **11g** (238 mg, 61%) as a white solid: mp >360°C; ¹H NMR ((CD₃)₂SO) (COSY) δ 6.86 (1 H, s, 4-H), 7.47 (1 H, m, 7-H), 7.52 (1 H, t, $J = 8.1$ Hz, 6-H), 7.67 (2 H, d, $J = 8.6$ Hz, Ph 2,6-H₂), 7.78 (2 H, d, $J = 8.6$ Hz, Ph 3,5-H₂), 8.03 (1 H, d, $J = 7.9$ Hz, 8-H), 11.87 (1 H, bs, N-H); ¹³C NMR ((CD₃)₂SO) δ (HSQC / HMBC) δ 94.61 (d, $J = 5.1$ Hz, 4-C), 117.08 (d, $J = 19.3$ Hz, 6-

C), 122.60 (d, $J = 3.5$ Hz, 8-C), 122.66 (Ph 4-C), 126.45 (d, $J = 7.9$ Hz, 7-C), 126.53 (8a-C), 126.80 (d, $J = 16.3$ Hz, 4a-C), 128.85 (Ph 3,5-C₂), 131.45 (Ph 2,6-C₂), 133.27 (Ph 1-C), 140.87 (3-C), 157.20 (d, $J = 248.3$ Hz, 5-C), 162.10 (1-C); ¹⁹F NMR ((CD₃)₂SO) δ -121.89 (m, F); MS m/z 317.9760 (M - H)⁻ (C₁₅H₈⁸¹BrFNO requires 317.9753), 315.9773 (M - H)⁻ (C₁₅H₈⁷⁹BrFNO requires 315.9773).

5-Fluoro-3-(pyridin-4-yl)isoquinolin-1-one (14h). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr₂NH (131 mg, 1.3 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **49** (200 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Cyanopyridine (114 mg, 1.1 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and washing (EtOH) gave **14h** (264 mg, 99%) as a white solid: mp >360°C; IR ν_{\max} 3435, 1675, 1244 cm⁻¹; ¹H NMR ((CD₃)₂SO) δ 7.10 (1 H, s, 4-H), 7.55 (1 H, m, 7-H), 7.64 (1 H, t, $J = 8.0$ Hz, 6-H), 7.86 (2 H, d, $J = 6.2$ Hz, pyridine 3,5-H₂), 8.06 (1 H, d, $J = 7.8$ Hz, 8-H), 8.70 (2 H, d, $J = 6.2$ Hz, pyridine 2,6-H₂), 11.90 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 96.61 (4-C), 117.89 (d, $J = 19.8$ Hz, 6-C), 121.10 (pyridine 3,5-C₂), 122.86 (8-C), 126.40 (d, $J = 15.9$ Hz, 4a-C), 127.26 (8a-C), 127.86 (d, $J = 7.9$ Hz, 7-C), 138.75 (3-C), 140.57 (pyridine 4-C), 150.19 (pyridine 2,6-C₂), 157.52 (d, $J = 248.8$ Hz, 5-C), 161.79 (1-C); ¹⁹F NMR ((CD₃)₂SO) δ -121.19 (m, F); MS m/z 239.0622 (M - H)⁻ (C₁₄H₈FN₂O requires 239.0621).

5-Methoxy-3-(4-methylphenyl)isoquinolin-1-one (15b). BuLi (1.6 M in hexanes, 0.8 mL, 1.3 mmol) was added to dry Pr₂NH (156 mg, 1.55 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (250 mg, 1.3 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Methylbenzonitrile (151 mg, 1.3 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and recrystallisation (EtOH) gave **15b** (16 mg, 5%) as pale yellow crystals: mp 249-251°C; ¹H NMR ((CD₃)₂SO) (COSY) δ 2.36 (3 H, s, Ph-Me), 3.94 (3 H, s, OMe), 6.92 (1 H, s, 4-H), 7.25 (1 H, dd, $J = 8.0, 0.9$ Hz, 6-H), 7.29 (2 H, d, $J = 7.9$ Hz, Ph 3,5-H₂), 7.41 (1 H, t, $J = 8.0$ Hz, 7-H), 7.66 (2 H, d, $J = 8.2$ Hz, Ph 2,6-H₂), 7.77 (1 H, dt, $J = 8.0, 0.8$ Hz, 8-H), 11.54 (1 H, br, N-H); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 20.81 (Me), 55.92 (OMe), 96.35 (4-C), 112.22 (6-C), 118.23 (8-C), 125.66 (4a-C), 126.51 (Ph 2,6-C₂), 126.64 (7-C), 128.52 (8a-C), 129.40 (Ph 3,5-C₂), 131.22 (Ph 1-C), 138.88 (3-C), 139.62 (Ph 4-C), 154.33 (5-C), 162.54 (1-C); MS m/z 288.0995 (M + Na)⁺ (C₁₇H₁₅NaNO₂ requires 288.1001).

3-(4-(1,1-Dimethylethyl)phenyl)-5-methoxyisoquinolin-1-one (15c). BuLi (2.5 M in hexanes, 0.42 mL, 1.0 mmol) was added to dry Pr₂NH (126 mg, 1.2 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (200 mg, 1.0 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-(1,1-Dimethylethyl)benzonitrile (164 mg, 1.0 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. H₂O (1.0 mL) was added and the mixture was diluted with CH₂Cl₂ and washed thrice with brine. Drying, evaporation and washing (EtOH) gave **15c** (72 mg, 23%) as a white solid: mp 249-250°C; IR ν_{\max} 3451, 1633 cm⁻¹; ¹H NMR ((CD₃)₂SO) (COSY) δ 1.33 (9 H, s, Bu^t), 3.96 (3 H, s, OMe), 6.95 (1 H, s, 4-H), 7.27 (1 H, d, $J = 7.9$ Hz, 6-H), 7.44 (1 H, t, $J = 8.0$ Hz, 7-H), 7.52 (2 H, d, $J = 8.5$ Hz, Ph 3,5-H₂), 7.72 (2 H, d, $J = 8.5$ Hz, Ph 2,6-H₂), 7.79 (1 H, d, $J = 8.0$ Hz, 8-H), 11.54 (1 H, br,

NH); ^{13}C NMR ((CD_3) $_2\text{SO}$) (HSQC / HMBC) δ 30.96 ($\text{C}(\text{CH}_3)_3$), 34.43 (CMe_3), 55.90 (OMe), 96.43 (4-C), 112.19 (6-C), 118.19 (8-C), 125.59 (Ph 3,5- C_2), 125.59 (8a-C), 126.30 (Ph 3,5- C_2), 126.63 (7-C), 128.46 (4a-C), 131.19 (Ph 1-C), 139.45 (3-C), 151.85 (Ph 4-C), 154.28 (5-C), 162.47 (1-C); MS m/z 308.1639 ($\text{C}_{20}\text{H}_{22}\text{NO}_2$ requires 308.1652).

5-Methoxy-3-(4-trifluoromethylphenyl)isoquinolin-1-one (15d). BuLi (1.6 M in hexanes, 0.8 mL, 1.3 mmol) was added to dry Pr^i_2NH (157 mg, 1.55 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (250 mg, 1.3 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 4-Trifluoromethylbenzonitrile (221 mg, 1.3 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was extracted with CH_2Cl_2 . The extract was washed thrice with brine and dried. Evaporation and recrystallisation (EtOH) gave **15d** (113 mg, 27%) as white crystals: mp $259\text{--}260^\circ\text{C}$; ^1H NMR ((CD_3) $_2\text{SO}$) (COSY) δ 3.95 (3 H, s, Me), 7.04 (1 H, s, 4-H), 7.30 (1 H, d, $J = 8.0$ Hz, 6-H), 7.48 (1 H, t, $J = 8.0$ Hz, 7-H), 7.80 (1 H, d, $J = 8.0$ Hz, 8-H), 7.83 (2 H, d, $J = 8.3$ Hz, Ph3,5- H_2), 7.98 (2 H, d, $J = 8.2$ Hz, Ph 2,6- H_2), 11.75 (1 H, bs, N-H); ^{13}C NMR ((CD_3) $_2\text{SO}$) (HSQC / HMBC) δ 55.93 (Me), 98.28 (4-C), 112.46 (6-C), 118.18 (8-C), 124.03 (q, $J = 270.5$ Hz, CF_3), 125.51 (q, $J = 3.8$ Hz, Ph 3,5- C_2), 126.15 (4a-C), 127.40 (7-C), 127.49 (Ph 2,6- C_2), 127.93 (8a-C), 129.14 (q, $J = 31.9$ Hz, Ph 4-C), 137.85 (Ph 1-C), 137.96 (3-C), 154.54 (5-C), 162.30 (1-C); ^{19}F NMR ((CD_3) $_2\text{SO}$) δ -61.20 (s, CF_3); MS m/z 318.0740 ($\text{M} - \text{H}^-$) ($\text{C}_{17}\text{H}_{11}\text{F}_3\text{NO}_2$ requires 318.0747).

3-(4-Chlorophenyl)-5-methoxyisoquinolin-1-one (15e). BuLi (1.6 M in hexanes, 0.8 mL, 1.3 mmol) was added to dry Pr^i_2NH (156 mg, 1.55 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (250 mg, 1.3 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 4-Chlorobenzonitrile (178 mg, 1.3 mmol) in dry THF (2.0 mL) was added -78°C and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 , washed thrice with brine and dried. Evaporation and washing (EtOH) gave **15e** (86 mg, 23%) as an off-white solid: mp $243\text{--}245^\circ\text{C}$; ^1H NMR ((CD_3) $_2\text{SO}$) (COSY) δ 4.00 (3 H, s, Me), 7.01 (1 H, s, 4-H), 7.33 (1 H, d, $J = 7.4$ Hz, 6-H), 7.50 (1 H, t, $J = 8.0$ Hz, 7-H), 7.60 (2 H, d, $J = 6.8$ Hz, Ph 3,5- H_2), 7.84 (3 H, m, 8-H + Ph 2,6- H_2), 11.71 (1 H, br, N-H); ^{13}C NMR ((CD_3) $_2\text{SO}$) (HSQC / HMBC) δ 55.95 (Me), 97.34 (4-C), 112.39 (6-C), 118.23 (8-C), 125.89 (4a-C), 127.11 (7-C), 128.20 (8a-C), 128.56 (Ph 2,6- C_2), 128.79 (Ph 3,5- C_2), 132.88 (Ph 1-C), 133.91 (Ph 4-C), 138.42 (3-C), 154.44 (5-C), 162.44 (1-C); MS m/z 308.0413 ($\text{M} + \text{Na}^+$) ($\text{C}_{16}\text{H}_{12}^{35}\text{ClNNaO}_2$ requires 308.0449).

3-(4-Bromophenyl)-5-methoxyisoquinolin-1-one (15f). BuLi (1.6 M in hexanes, 0.70 mL, 1.1 mmol) was added to dry Pr^i_2NH (131 mg, 1.3 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (200 mg, 1.0 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C . 4-Bromobenzonitrile (188 mg, 1.0 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C , then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH_2Cl_2 , washed thrice with brine and dried. Evaporation and washing (EtOH) gave **15f** (48 mg, 14%) as a white solid: mp $263\text{--}264^\circ\text{C}$; IR ν_{max} 3526, 1665, 739 cm^{-1} ; ^1H NMR ((CD_3) $_2\text{SO}$) δ 3.94 (3 H, s, Me), 6.95 (1 H, s, 4-H), 7.27 (1 H, d, $J = 7.8$ Hz, 6-H), 7.45 (1 H, t, $J = 8.0$ Hz, 7-H), 7.69 (4 H, m, Ph 2,3,5,6- H_4), 7.78 (1 H, d, $J = 8.0$ Hz, 8-H), 11.64 (1 H, br, NH); ^{13}C NMR ((CD_3) $_2\text{SO}$) (HSQC / HMBC) δ 55.95 (Me), 97.30 (4-C), 112.39 (6-C), 118.23 (8-C), 122.58 (Ph 4-C), 125.90 (4a-C), 127.11 (7-C), 128.19 (8a-C), 128.79 (Ph 2,6- C_2), 131.70 (Ph 3,5-

C₂), 133.24 (Ph 1-C), 138.49 (3-C), 154.44 (5-C), 162.44 (1-C); MS *m/z* 682.9978 (2 M + Na) (C₃₂H₂₄⁷⁹Br⁸¹BrN₂NaO₄ requires 682.9981); 661.0145 (2 M + H) (C₃₂H₂₅⁷⁹Br⁸¹BrN₂O₄ requires 661.0161); 351.9959 (M + Na) (C₁₆H₁₂⁷⁹BrNNaO₂ requires 351.9949); 332.0098 (M + H)⁺ (C₁₆H₁₃⁸¹BrNO₂ requires 332.0110); 330.0113 (M + H)⁺ (C₁₆H₁₃⁷⁹BrNO₂ requires 330.0130).

5-Methoxy-3-(pyridin-4-yl)isoquinolin-1-one (15g). BuLi (1.6 M in hexanes, 0.80 mL, 1.3 mmol) was added to dry Pr₂NH (157 mg, 1.55 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (250 mg, 1.3 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 4-Cyanopyridine (135 mg, 1.3 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. Water (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and washing (EtOH) gave **15g** (284 mg, 87%) as a white solid: mp >360°C; IR *v*_{max} 3431, 1673 cm⁻¹; ¹H NMR ((CD₃)₂SO) (COSY) δ 3.96 (3 H, s, Me), 7.16 (1 H, s, 4-H), 7.31 (1 H, d, *J* = 7.9 Hz, 6-H), 7.50 (1 H, t, *J* = 8.0 Hz, 7-H), 7.80 (3 H, m, 8-H + pyridine 3,5-H₂), 8.66 (2 H, d, *J* = 6.1 Hz, pyridine 2,6-H₂), 11.74 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC) δ 56.04 (Me), 98.74 (4-C), 112.64 (6-C), 118.26 (8-C), 120.76 (pyridine 3,5-C₂), 126.55 (4a-C), 127.70 (8a-C), 127.93 (7-C), 136.82 (pyridine 4-C), 140.86 (3-C), 150.19 (pyridine 2,6-C₂), 154.70 (5-C), 162.39 (1-C); MS *m/z* 253.0972 (M + H) (C₁₅H₁₃N₂O₂ requires 253.0977).

3-(Benzo-1,3-dioxol-5-yl)-5-methoxyisoquinolin-1-one (15h). BuLi (1.6 M in hexanes, 0.7 mL, 1.1 mmol) was added to dry Pr₂NH (125 mg, 1.2 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (200 mg, 1.0 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 5-Cyanobenzo-1,3-dioxole (152 mg, 1.0 mmol) in dry THF (2.0 mL) was added at -78 °C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. H₂O (1.0 mL) was added. The mixture was diluted with CH₂Cl₂, washed thrice with brine and dried. Evaporation and washing (EtOH) gave **15h** (32 mg, 11%) as an off-white solid: mp 282-284°C; IR *v*_{max} 3445, 1631 cm⁻¹; ¹H NMR ((CD₃)₂SO) δ 3.93 (3 H, s, Me), 6.09 (2 H, s, CH₂), 6.86 (1 H, s, 4-C), 7.01 (1 H, d, *J* = 8.1 Hz, Ph 5-H), 7.25 (1 H, d, *J* = 7.2 Hz, 6-H), 7.27 (1 H, dd, *J* = 8.2, 1.9 Hz, Ph 6-H), 7.33 (1 H, d, *J* = 1.8 Hz, Ph 2-H), 7.40 (1 H, t, *J* = 8.0 Hz, 7-H), 7.74 (1 H, d, *J* = 8.0 Hz, 8-H), 11.45 (1 H, br, NH); ¹³C NMR ((CD₃)₂SO) (HSQC / HMBC / DEPT) δ 55.91 (OMe), 96.29 (4-C), 101.53 (CH₂), 107.03 (Ph 4-C), 108.54 (Ph 7-C), 112.17 (6-C), 118.21 (8-C), 120.92 (Ph 6-C), 125.54 (4a-C), 126.52 (7-C), 128.20 (Ph 5-C), 128.54 (8a-C), 139.42 (3-C), 147.72 (Ph 7a-C), 148.16 (Ph 3a-C), 154.27 (5-C), 162.51 (1-C); MS *m/z* 613.1595 (2 M + Na) (C₃₄H₂₆N₂NaO₈ requires 613.1587); 591.1768 (2 M + H) (C₃₄H₂₇N₂O₈ requires 591.1767); 318.0765 (M + Na) (C₁₇H₁₃NNaO₄ requires 318.0742); 296.0907 (M + H) (C₁₇H₁₄NO₄ requires 296.0923).

5-Methoxy-3-(thiophen-3-yl)isoquinolin-1-one (15i). BuLi (2.5 M in hexanes, 0.42 mL, 1.0 mmol) was added to dry Pr₂NH (126 mg, 1.24 mmol) in dry THF (2.0 mL) at -78°C and the mixture was stirred at -78°C for 10 min. Compound **51** (200 mg, 1.0 mmol) in dry THF (2.0 mL) was added and the mixture was stirred for 1 h at -78°C. 3-Cyanothiophene (112 mg, 1.0 mmol) in dry THF (2.0 mL) was added at -78°C and the mixture was stirred for 1 h at -78°C, then at 20°C for 16 h. H₂O (1.0 mL) was added. The mixture was diluted with CH₂Cl₂ and washed thrice with brine. Evaporation and washing (EtOH) gave **15i** (37 mg, 14%) as a pale buff solid: mp 286-287°C; IR *v*_{max} 3503, 1652, 746 cm⁻¹; ¹H NMR ((CD₃)₂SO) (COSY) δ 3.94 (3 H, s, Me), 7.04 (1 H, s, 4-H), 7.24 (1 H, d, *J* = 7.9 Hz, 6-H), 7.40 (1 H, t, *J* = 8.0 Hz, 7-H), 7.66 (2 H, m, thiophene 4,5-H₂), 7.75 (1 H, d, *J* = 8.0 Hz, 8-H), 8.23 (1 H, d, *J* = 1.2

Hz, thiophene 2-H), 11.48 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 55.88 (Me), 95.99 (4-C), 112.28 (6-C), 118.24 (8-C), 123.36 (thiophene 2-C), 125.71 (8a-C), 125.78 (thiophene 5-C), 126.63 (7-C), 127.44 (thiophene 4-C), 128.44 (4a-C), 134.71 (thiophene 1-C), 135.20 (3-C), 154.30 (5-C), 162.29 (1-C); MS m/z 280.0399 ($\text{C}_{14}\text{H}_{11}\text{NNaO}_2\text{S}$ requires 280.0409).

5-Hydroxy-3-(4-trifluoromethylphenyl)isoquinolin-1-one (16b). Compound **15d** (51 mg, 0.16 mmol) was heated with BBr_3 in CH_2Cl_2 (1.0 M, 4.0 mL) at reflux for 16 h. The evaporation residue was treated with aq. NaOH (2.5 M, 3.5 mL) at 0°C and the mixture was stirred at 20°C for 3 h. The solution was acidified with aq. HCl (2 M). The solid was collected by filtration. Chromatography (EtOAc / petroleum ether 2:3 \rightarrow 1:1) gave **16b** (3.9 mg, 8%) as a pale buff solid: mp $258\text{--}260^\circ\text{C}$; IR ν_{max} 3399, 3197, 1640, 1329, 1113, 1068 cm^{-1} ; ^1H NMR (CD_3OD) δ 7.14 (1 H, dd, $J = 7.8, 1.0$ Hz, 6-H), 7.29 (1 H, s, 4-H), 7.37 (1 H, t, $J = 7.9$ Hz, 7-H), 7.81 (3 H, m, 8-H + Ph 3,5- H_2), 7.92 (2 H, d, $J = 8.2$ Hz, Ph 2,6- H_2); ^{13}C NMR (CD_3OD) (HSQC / HMBC) δ 102.03 (4-C), 117.66 (6-C), 118.54 (8-C), 125.54 (q, $J = 268.9$ Hz, CF_3), 126.94 (q, $J = 3.8$ Hz, Ph 3,5- C_2), 127.41 (4a-C), 128.36 (Ph 2,6- C_2), 128.90 (7-C), 129.23 (8a-C), 131.88 (q, $J = 32.4$ Hz, Ph 4-C), 138.33 (3-C), 139.73 (Ph 1-C), 154.84 (5-C), 165.60 (1-C); MS m/z 328.0568 ($(\text{M} + \text{Na})^+$ ($\text{C}_{16}\text{H}_{10}\text{F}_3\text{NNaO}_2$ requires 328.0561), 306.0740 ($(\text{M} + \text{H})^+$ ($\text{C}_{16}\text{H}_{11}\text{F}_3\text{NO}_2$ requires 306.0742); MS m/z 304.0577 ($(\text{M} - \text{H})^-$ ($\text{C}_{16}\text{H}_9\text{F}_3\text{NO}_2$ requires 304.0585).

5-Nitro-3-(4-trifluoromethylphenyl)isoquinolin-1-one (22i). Compound **30i** (78 mg, 220 μmol) was stirred with HBr in AcOH (33%, 3.5 mL) at 65°C for 7 h. Evaporation yielded **22i** (34.5 mg, 47%) as a yellow solid: mp: $292\text{--}294^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 7.30 (1 H, s, 4-H), 7.70 (1 H, t, $J = 8.0$ Hz, 7-H), 7.89 (2 H, d, $J = 8.5$ Hz, Ph 3,5- H_2), 7.99 (2 H, d, $J = 8.5$ Hz, Ph 2,6- H_2), 8.49 (1 H, d, $J = 7.5$ Hz, 8-H), 8.60 (1 H, d, $J = 7.5$ Hz, 6-H), 12.26 (1 H, br, N-H); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 98.63 (4-C), 124.01 (q, $J = 270.8$ Hz, CF_3), 125.81 (q, $J = 3.6$ Hz, Ph 3,5- C_2), 126.36 (7-C), 126.89 (8a-C), 128.27 (Ph 2,6- C_2), 129.99 (8-C), 130.04 (q, $J = 31.8$ Hz, Ph 4-C), 130.59 (4a-C), 133.19 (6-C), 137.44 (Ph 1-C), 142.64 (3-C), 144.94 (5-C), 161.33 (1-C); ^{19}F NMR ($(\text{CD}_3)_2\text{SO}$) δ -61.22 (s, CF_3); MS m/z 333.0493 ($(\text{M} - \text{H})^-$ ($\text{C}_{16}\text{H}_8\text{F}_3\text{N}_2\text{O}_3$ requires 333.0493).

3-(4-Fluorophenyl)-5-nitroisoquinolin-1-one (22j). Compound **30j** (16 mg, 50 μmol) was stirred with HBr in AcOH (33%, 1.0 mL) at 65°C for 7 h. Evaporation yielded **22j** (7.8 mg, 55%) as a yellow solid: mp $>360^\circ\text{C}$; ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 7.19 (1 H, s, 4-H), 7.36 (2 H, t, $J = 8.6$ Hz, Ph 3,5- H_2), 7.65 (1 H, $J = 7.9$ Hz, 7-H), 7.84 (2 H, dd, $J = 8.2, 5.3$ Hz, Ph 2,6- H_2), 8.46 (1 H, d, $J = 7.8$ Hz, 8-H), 8.59 (1 H, d, $J = 7.7$ Hz, 6-H), 11.95 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 96.94 (4-C), 115.56 (d, $J = 21.8$ Hz, Ph 3,5- C_2), 125.41 (7-C), 126.38 (8a-C), 129.36 (8-C), 129.43 (Ph 2,6- C_2), 129.86 (4a-C), 130.63 (Ph 1-C), 132.83 (6-C), 143.07 (3-C), 144.55 (5-C), 160.99 (1-C), 162.94 (d, $J = 246.6$ Hz, Ph 4-C); ^{19}F NMR ($(\text{CD}_3)_2\text{SO}$) δ -110.96 (m, F); MS m/z 283.0524 ($(\text{M} - \text{H})^-$ ($\text{C}_{15}\text{H}_8\text{FN}_2\text{O}_3$ requires 283.0524).

1,3-Dichloro-5-nitroisoquinoline (27). Aq. HNO_3 (67%, 430 mg) in conc. H_2SO_4 (3.0 mL) was added dropwise to 1,3-dichloroisoquinoline **26** (1.00 g, 5.1 mmol) in conc. H_2SO_4 (5.0 mL) at 5°C . The mixture was stirred at $0\text{--}5^\circ\text{C}$ for 2 h, then poured onto ice. The precipitate was collected, washed (H_2O), dried and recrystallised (EtOAc / petroleum ether) to give **27** (1.12 g, 91%) as a yellow powder: mp $168\text{--}170^\circ\text{C}$ (lit.² mp $168\text{--}170^\circ\text{C}$); ^1H NMR (CDCl_3) δ 7.80 (1 H, t, $J = 7.8$ Hz, 7-H), 8.55 (1 H, s, 4-H), 8.62 (1 H, dd, $J = 7.8, 1.8$ Hz, 6-H), 8.72 (1 H, dt, $J = 8.5, 1.1$ Hz, 8-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 115.16 (4-C), 126.00 (4a-

C), 126.64 (7-C), 129.63 (6-C), 131.60 (8a-C), 133.12 (8-C), 144.01 (5-C), 147.08 (3-C), 151.75 (1-C).

1-Methoxy-3-(3-methylphenyl)-5-nitroisoquinoline (30b). Compound **28** (0.84 g, 3.5 mmol), Pd₂dba₃ (0.18 g, 0.35 mmol), SPhos (0.14 g, 0.70 mmol), K₃PO₄ (1.5 g, 7.1 mmol) and 3-methylphenylboronic acid (720 mg 5.3 mmol) were placed in a dry flask. Degassed toluene (20 mL) was added and the mixture was stirred at 100°C for 16 h. Evaporation and chromatography (hexane / EtOAc 15:1) gave **30b** (700 mg, 67%) as yellow crystals: mp 166-169°C; ¹H NMR (CDCl₃) δ 2.36 (3 H, s, ArMe), 4.11 (3 H, s, OMe), 7.13 (1 H, d, *J* = 7.8 Hz, Ar 4-H), 7.27 (1 H, t, *J* = 7.8 Hz, Ar 5-H), 7.36 (1 H, t, *J* = 7.4 Hz, 7-H), 7.83 (1 H, s, Ar 2-H), 7.85 (1 H, d, *J* = 7.6 Hz Ar 6-H), 8.23-8.26 (2 H, m, 6-H and 4-H), 8.39 (1 H, d, *J* = 7.4 Hz 8-H); ¹³C NMR (HMBC / HMQC) δ 21.6 (ArMe), 54.0 (OMe), 104.9 (4-C), 124.2 (Ar 6-C), 124.2 (7-C), 127.6 (Ar 2-C) 128.5 (6-C), 128.6 (Ar 5-C), 130.1 (Ar 4-C), 131.1 (8-C), 131.3 (C_q), 138.2 (Ar 1-C), 138.5 (C_q), 151.8 (3-C), 151.9 (5-C), 160.3 (1-C); MS *m/z* 295.1076 (M + H)⁺ (C₁₇H₁₅N₂O₃ requires 295.1083).

1-Methoxy-3-(2-methoxyphenyl)-5-nitroisoquinoline (30d). Degassed PhMe (3.0 mL) was added to **28** (102 mg, 430 μmol), Pd₂dba₃ (11.5 mg, 13 μmol), SPhos (23 mg, 56 μmol), 2-methoxybenzeneboronic acid (150 mg, 1.0 mmol) and K₃PO₄ (204 mg, 1.0 mmol) in a dry flask. The mixture was stirred at 100°C for 16 h. The evaporation residue, in CHCl₃, was filtered. Chromatography (EtOAc / petroleum ether 1:99) gave **30d** (74 mg, 58%) as a yellow solid: mp 115-117°C; ¹H NMR (CDCl₃) δ 3.97 (3 H, s, PhOMe), 4.23 (3 H, s, 1-OMe), 7.06 (1 H, d, *J* = 8.3 Hz, Ph 3-H), 7.11 (1 H, td, *J* = 7.6, 1.1 Hz, Ph 4-H), 7.39 (1 H, td, *J* = 7.8, 1.8 Hz, Ph 5-H), 7.55 (1 H, t, *J* = 7.9 Hz, 7-H), 8.15 (1 H, dd, *J* = 7.8, 1.8 Hz, Ph 6-H), 8.43 (1 H, dd, *J* = 7.8, 1.3 Hz, 6-H), 8.59 (1 H, dt, *J* = 8.2, 1.1 Hz, 8-H), 8.78 (1 H, s, 4-H); ¹³C NMR (CDCl₃) (HSQC / HMBC) δ 54.06 (1-OMe), 55.71 (PhOMe), 110.12 (4-C), 111.79 (Ph 3-C), 119.70 (8a-C), 120.87 (Ph 4-C), 124.36 (7-C), 128.18 (6-C), 130.17 (Ph 5-C), 130.91 (8-C), 131.22 (Ph 6-C), 146.81 (5-C), 157.82 (Ph 2-C), 160.04 (1-C); MS *m/z* 333.0858 (M + Na)⁺ (C₁₇H₁₄N₂NaO₄ requires 333.0852), 311.1030 (M + H)⁺ (C₁₇H₁₅N₂O₄ requires 311.1034).

1-Methoxy-3-(3-methoxyphenyl)-5-nitroisoquinoline (30e). Degassed PhMe (3.0 mL) was added to **28** (103 mg, 430 μmol), Pd₂dba₃ (11.6 mg, 13 μmol), SPhos (22 mg, 54 μmol), 3-methoxybenzeneboronic acid (153 mg, 1.0 mmol) and K₃PO₄ (203 mg, 0.96 mmol). The mixture was stirred at 100°C for 16 h. The evaporation residue, in CHCl₃, was filtered. Chromatography (EtOAc / petroleum ether 1:99) gave **30e** (81 mg, 81%) as a yellow solid: mp 87-90°C; ¹H NMR (CDCl₃) δ 3.93 (3 H, s, PhOMe), 4.28 (3 H, s, 1-OMe), 7.00 (1 H, m, Ph 6-H), 7.42 (1 H, t, *J* = 8.0 Hz, Ph 5-H), 7.57 (1 H, t, *J* = 8.0 Hz, 7-H), 7.78 (2 H, m, Ph 2,4-H₂), 8.48 (1 H, dd, *J* = 7.8, 1.3 Hz, 6-H), 8.51 (1 H, s, 4-H), 8.61 (1 H, dt, *J* = 8.2, 1.0 Hz, 8-H); ¹³C NMR (CDCl₃) (HSQC / HMBC) δ 54.16 (PhOMe), 56.00 (1-OMe), 105.38 (4-C), 112.98 (Ph 4-C), 114.79 (Ph 6-C), 119.62 (Ph 2-C), 124.53 (7-C), 128.54 (6-C), 129.76 (Ph 5-C), 131.20 (8-C), 139.72 (Ph 3-C), 144.35 (5-C), 160.26 (1-C); MS *m/z* 311.1030 (M + H)⁺ (C₁₇H₁₅N₂O₄ requires 311.1034).

1-Methoxy-5-nitro-3-(3-trifluoromethylphenyl)isoquinoline (30h). Method A. Degassed PhMe (3.0 mL) was added to **28** (101 mg, 420 μmol), Pd₂dba₃ (41 mg, 45 μmol), SPhos (40 mg, 100 μmol), 3-trifluoromethylbenzeneboronic acid (161 mg, 850 μmol) and K₃PO₄ (179 mg, 840 μmol). The mixture was stirred at 100°C for 16 h. The evaporation residue, in CHCl₃, was filtered. Chromatography (Et₂O / petroleum ether 1:199) gave **30h** (80.4 mg, 55%) as a yellow solid: mp 135-137°C; ¹H NMR (CDCl₃) δ 4.29 (3 H, s, Me), 7.62 (2 H, m, 7-H + Ph 5-H), 7.70 (1 H, d, *J* = 8.0 Hz, Ph 4-H), 8.34 (1 H, d, *J* = 7.9 Hz, Ph 6-H), 8.47 (1

H, s, Ph 2-H), 8.49 (1 H, dd, $J = 7.7, 1.2$ Hz, 6-H), 8.53 (1 H, s, 4-H), 8.62 (1 H, dt, $J = 7.2, 1.0$ Hz, 8-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 54.31 (Me), 105.70 (4-C), 120.30 (8a-C), 123.98 (q, $J = 3.9$ Hz, Ph 2-C), 124.19 (q, $J = 270.4$ Hz, CF_3), 125.08 (7-C), 125.84 (q, $J = 3.9$ Hz, Ph 4-C), 126.89, 128.77 (6-C), 128.78, 29.20 (Ph 5-C), 130.12 (Ph 6-C), 131.27 (8-C), 131.27 (4a-C), 131.30 (q, $J = 32.3$ Hz, Ph 3-C), 139.47 (Ph 1-C), 145.04 (5-C), 150.25 (3-C), 160.75 (1-C); ^{19}F NMR (CDCl_3) δ -62.66 (s, CF_3); MS m/z 349.0826 ($\text{M} + \text{H}$)⁺ ($\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_2\text{O}_3$ requires 349.0802).

1-Methoxy-5-nitro-3-(3-trifluoromethylphenyl)isoquinoline (30h). Method B. Dry DMF (8.0 mL) was added to **37** (300 mg, 1.1 mmol), Pd_2dba_3 (97 mg, 106 μmol), SPhos (99 mg, 0.21 mmol), 3-trifluoromethylbenzeneboronic acid (403 mg, 2.1 mmol) and K_3PO_4 (675 mg, 3.2 mmol) and the mixture was stirred at 135°C for 16 h. The mixture was filtered (Celite®) and the solvent was evaporated. Chromatography (EtOAc / petroleum ether 1:49) gave **30h** (232 mg, 63%) as a yellow solid, with properties as above.

1-Methoxy-5-nitro-3-(4-trifluoromethylphenyl)isoquinoline (30i). To **37** (300 mg, 1.1 mmol) in a dry flask was added Pd_2dba_3 (97 mg, 110 μmol), SPhos (99 mg, 210 μmol), 4-trifluoromethylphenylbenzeneboronic acid (403 mg, 2.1 mmol) and K_3PO_4 (675 mg, 3.2 mmol). Dry DMF (8.0 mL) was added and the mixture was stirred at 135°C for 16 h. The mixture was filtered through Celite® and the solvent was evaporated. Chromatography (EtOAc / petroleum ether 3:197) gave **30i** (209 mg, 57%) as a yellow solid: mp 125-127°C; ^1H NMR (CDCl_3) δ 4.25 (3 H, s, Me), 7.58 (1 H, t, $J = 7.9$ Hz, 7-H), 7.72 (2 H, d, $J = 8.2$ Hz, Ph 3,5- H_2), 8.25 (2 H, d, $J = 8.1$ Hz, Ph 2,6- H_2), 8.46 (1 H, dd, $J = 7.8, 1.3$ Hz, 6-H), 8.50 (1 H, s, 4-H), 8.58 (1 H, dt, $J = 8.2, 1.1$ Hz, 8-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 54.23 (Me), 105.94 (4-C), 120.18 (4a-C), 125.11 (7-C), 125.57 (q, $J = 3.6$ Hz, Ph 3,5- C_2), 126.42 (q, $J = 275.0$ Hz, CF_3), 127.20 (Ph 2,6- C_2), 128.75 (6-C), 131.17 (8a-C), 131.20 (8-C), 141.79 (Ph 1-C), 144.82 (5-C), 150.01 (3-C), 160.56 (1-C); ^{19}F NMR (CDCl_3) δ -62.56 (s, CF_3); MS m/z 371.0601 ($\text{M} + \text{Na}$)⁺ ($\text{C}_{17}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_3\text{Na}$ requires 371.0622), 349.0775 ($\text{M} + \text{H}$)⁺ ($\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_2\text{O}_3$ requires 349.0780).

3-(4-Fluorophenyl)-1-methoxy-5-nitroisoquinoline (30j). To **37** (200 mg, 710 μmol) in a dry flask was added Pd_2dba_3 (65 mg, 70 μmol), SPhos (66 mg, 140 μmol), 4-fluorobenzeneboronic acid (148 mg, 1.1 mmol) and K_3PO_4 (448 mg, 2.1 mmol). Dry DMF (6.0 mL) was added and the mixture was stirred at 135°C for 16 h. The evaporation residue, in CHCl_3 , was filtered through Celite®. Chromatography (EtOAc / petroleum ether 1:99 \rightarrow 1:49) gave **30j** (60 mg, 28%) as a yellow solid: mp 199-200°C; ^1H NMR (CDCl_3) δ 4.27 (3 H, s, Me), 7.19 (2 H, t, $J = 8.5$ Hz, Ph 3,5- H_2), 7.57 (1 H, t, $J = 8.0$ Hz, 7-H), 8.19 (2 H, m, Ph 2,6- H_2), 8.47 (1 H, s, 4-H), 8.49 (1 H, dd, $J = 8.0, 1.0$ Hz, 6-H), 8.61 (1 H, d, $J = 8.0$ Hz; ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 54.11 (Me), 104.79 (4-C), 115.68 (d, $J = 21.5$ Hz, Ph 3,5- C_2), 119.91 (4a-C), 124.53 (7-C), 128.72 (6-C), 128.97 (d, $J = 8.3$ Hz, Ph 2,6- C_2), 131.26 (8-C), 131.56 (8a-C), 134.81 (Ph 1-C), 144.91 (5-C), 150.93 (3-C), 160.58 (1-C), 163.75 (d, $J = 248.3$ Hz, Ph 4-C); MS m/z 299.0808 ($\text{M} + \text{H}$)⁺ ($\text{C}_{16}\text{H}_{12}\text{FN}_2\text{O}_3$ requires 299.0834).

3-(2-Chlorophenyl)-1-methoxy-5-nitroisoquinoline (30k). Method A. To **28** (102 mg, 0.43 mmol) were added $\text{Pd}_2(\text{dba})_3$ (13 mg, 14 μmol), SPhos (22 mg, 54 μmol), 2-chlorobenzeneboronic acid (202 mg, 1.3 mmol) and K_3PO_4 (202 mg, 0.95 mmol). Degassed PhMe (3.0 mL) was added and the mixture was stirred at 100°C. After 4.5 h, further $\text{Pd}_2(\text{dba})_3$ (33.5 mg, 40 μmol) and SPhos (20.5 mg, 40 μmol) were added and the mixture was stirred at 100°C for a further 11.5 h. The evaporation residue, in CHCl_3 , was filtered. Chromatography (EtOAc / petroleum ether 1:99) gave **30k** (135 mg, 100%) as a yellow solid, with properties as below.

3-(2-Chlorophenyl)-1-methoxy-5-nitroisoquinoline (30k). Method B. To **37** (200 mg, 710 μmol) were added Pd_2dba_3 (65 mg, 70 μmol), SPhos (66 mg, 140 μmol), 2-chlorobenzeneboronic acid (165 mg, 1.1 mmol) and K_3PO_4 (450 mg, 2.1 mmol). Dry DMF (7.5 mL) was added and the mixture was stirred at 135°C for 16 h. The solvent was evaporated. The residue, in CHCl_3 , was filtered through Celite®. Chromatography (EtOAc / petroleum ether 3:197 \rightarrow 1:19) gave **30k** (132 mg, 60%) as a yellow solid: mp 122-127°C; ^1H NMR (CDCl_3) δ 4.21 (3 H, s, Me), 7.39 (1 H, t, J = 7.2 Hz, Ph 5-H), 7.40 (1 H, t, J = 7.0 Hz, Ph 4-H), 7.53 (1 H, dd, J = 7.5, 1.5 Hz, Ph 6-H), 7.63 (1 H, t, J = 7.9 Hz, 7-H), 7.73 (1 H, dd, J = 7.8, 1.7 Hz, Ph 3-H), 8.37 (1 H, s, 4-H), 8.49 (1 H, dd, J = 7.8, 1.3 Hz, 6-H), 8.65 (1 H, dt, J = 8.2, 1.1 Hz, 8-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 54.39 (Me), 110.19 (4-C), 119.79 (8a-C), 125.05 (7-C), 126.84 (Ph 4-C), 128.46 (6-C), 129.62 (Ph 5-C), 130.48 (Ph 6-C), 130.74 (4a-C), 131.13 (8-C), 131.67 (Ph 3-C), 144.95 (5-C), 160.29 (1-C); MS m/z 315.0533 ($\text{M} + \text{H}^+$) ($\text{C}_{16}\text{H}_{12}^{35}\text{ClN}_2\text{O}_3$ requires 315.0538).

3-(3-Chlorophenyl)-1-methoxy-5-nitroisoquinoline (30l). Method A. To **28** (104 mg, 0.44 mmol) in a dry flask was added $\text{Pd}_2(\text{dba})_3$ (44.0 mg, 48 μmol), SPhos (40.3 mg, 98 μmol), 3-chlorobenzeneboronic acid (198 mg, 1.3 mmol) and K_3PO_4 (180 mg, 0.85 mmol). Degassed toluene (3.0 mL) was added and the mixture was stirred at 100°C for 40 h. The evaporation residue, in CHCl_3 , was filtered. Chromatography (Et₂O / petroleum ether 1: 99) gave **30l** (46 mg, 34%) as a yellow solid, with properties as below.

3-(3-Chlorophenyl)-1-methoxy-5-nitroisoquinoline (30l). Method B. To **37** (200 mg, 710 μmol) were added Pd_2dba_3 (65 mg, 70 μmol), SPhos (66 mg, 140 μmol), 3-chlorobenzeneboronic acid (166 mg, 1.1 mmol) and K_3PO_4 (450 mg, 2.1 mmol). Dry DMF (7.5 mL) was added and the mixture was stirred at 135°C for 16 h. The solvent was evaporated. The residue, in CHCl_3 , was filtered through Celite®. Chromatography (EtOAc / petroleum ether 3:197 \rightarrow 1:19) gave **30l** (116 mg, 52%) as a yellow solid: mp 134-141°C; ^1H NMR (CDCl_3) δ 4.18 (3 H, s, Me), 7.41 (2 H, m, Ph 5,6-H₂), 7.58 (1 H, t, J = 8.0 Hz, 7-H), 8.03 (1 H, dt, J = 6.9, 1.9 Hz, Ph 4-H), 8.18 (1 H, s, Ph 2-H), 8.47 (1 H, dd, J = 7.8, 1.2 Hz, 6-H), 8.48 (1 H, s, 4-H), 8.60 (1 H, dt, J = 8.2, 1.1, 8-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 54.29 (Me), 105.53 (4-C), 120.18 (8a-C), 124.90 (7-C), 125.05 (Ph 4-C), 127.21 (Ph 2-C), 128.73 (6-C), 129.24 (Ph 6-C), 129.93 (Ph 5-C), 131.26 (8-C), 131.33 (4a-C), 134.81 (Ph 3-C), 140.43 (3a-C), 144.95 (5-C), 150.30 (3-C), 160.58 (1-C); MS m/z 315.0529 ($\text{M} + \text{H}^+$) ($\text{C}_{16}\text{H}_{12}^{35}\text{ClN}_2\text{O}_3$ requires 315.0538).

3-(4-Chlorophenyl)-1-methoxy-5-nitroisoquinoline (30m). Degassed toluene (3.0 mL) was added to **37** (96 mg, 0.34 mmol), $\text{Pd}_2(\text{dba})_3$ (31 mg, 34 μmol), SPhos (31.5 mg, 68 μmol), 4-chlorobenzeneboronic acid (79.3 mg, 0.51 mmol) and K_3PO_4 (215 mg, 1.01 mmol). The mixture was stirred at 100°C for 16 h. The evaporation residue, in CHCl_3 , was filtered (Celite®). Chromatography (EtOAc / petroleum ether 1:39) gave **30m** (104 mg, 98%) as a yellow solid: mp 168-169°C; ^1H NMR (CDCl_3) δ 4.24 (3 H, s, Me), 7.46 (2 H, dd, J = 6.8, 2.0 Hz, Ph 2,6-H₂), 7.56 (1 H, t, J = 7.9 Hz, 7-H), 8.13 (2 H, dd, J = 6.8, 2.0 Hz, Ph 3,5-H₂), 8.46 (1 H, dd, J = 7.7, 1.2 Hz, 6-H), 8.47 (1 H, s, 4-H), 8.59 (1 H, dt, J = 8.2, 0.92 Hz, 8-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 54.15 (Me), 105.06 (4-C), 120.04 (4a-C), 124.66 (7-C), 128.31 (Ph 3,5-C₂), 128.65 (6-C), 128.87 (Ph 2,6-C₂), 131.18 (8-C), 131.29 (8a-C), 135.41 (Ph 4-C), 137.07 (3-C), 150.67 (5-C), 160.81 (1-C); MS m/z 315.0531 ($\text{M} + \text{H}^+$) ($\text{C}_{16}\text{H}_{11}^{35}\text{ClN}_2\text{O}_3$ requires 315.0536).

3-(2,6-Dichlorophenyl)-1-methoxy-5-nitroisoquinoline (30n). To **37** (240 mg, 850 μmol) was added Pd_2dba_3 (78 mg, 85 μmol), SPhos (79 mg, 170 μmol), 2,6-dichlorobenzeneboronic

acid (243 mg, 1.3 mmol) and K_3PO_4 (541 mg, 2.5 mmol). Dry DMF (8.0 mL) was added and the mixture was stirred at 135°C for 16 h. Filtration (Celite®), evaporation and chromatography (EtOAc / petroleum ether 1: 99) gave **30n** (35 mg, 12%) as a yellow solid: mp 122-124°C; 1H NMR ($CDCl_3$) δ 4.17 (3 H, s, Me), 7.30 (1 H, t, J = 8.7 Hz, Ph 4-H), 7.44 (2 H, d, J = 8.5 Hz, Ph 3,5- H_2), 7.66 (1 H, t, J = 8.1 Hz, 7-H), 8.08 (1 H, s, 4-H), 8.52 (1 H, dd, J = 7.8, 1.3 Hz, 6-H), 8.67 (1 H, dt, J = 8.2, 1.1 Hz, 8-H); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 54.61 (Me), 111.16 (4-C), 120.08 (4a-C), 125.36 (7-C), 128.24 (Ph 3,5- C_2), 128.56 (6-C), 129.82 (Ph 4-C), 130.75 (8a-C), 131.32 (8-C), 134.86 (Ph 2,6- C_2), 138.19 (Ph 1-C), 144.94 (5-C), 149.95 (3-C), 160.73 (1-C); MS m/z 348.9740 ($M - H$)⁻ ($C_{16}H_{11}^{35}Cl^{37}ClN_2O_3$ requires 348.9961).

3-(3-Cyanophenyl)-1-methoxy-5-nitroisoquinoline (30q). Method A. To **37** (152 mg, 0.64 mmol) in a dry flask was added $Pd_2(dba)_3$ (58.3 mg, 64 μ mol), SPhos (60.8 mg, 0.15 mmol), 3-cyanobenzeneboronic acid (147 mg, 1.3 mmol) and K_3PO_4 (270 mg, 1.3 mmol). Degassed toluene (4.5 mL) was added and the mixture was stirred at 100°C for 16 h. The evaporation residue, in $CHCl_3$, was filtered. Chromatography (EtOAc / petroleum ether 1:40) gave **30q** (15.6 mg, 8%) as a yellow solid, with properties as below.

3-(3-Cyanophenyl)-1-methoxy-5-nitroisoquinoline (30q). Method B. To **37** (200 mg, 710 μ mol) were added Pd_2dba_3 (65 mg, 70 μ mol), SPhos (66 mg, 140 μ mol), 3-cyanobenzeneboronic acid (148 mg, 1.1 mmol) and K_3PO_4 (448 mg, 2.1 mmol). Dry DMF (6.0 mL) was added and the mixture was stirred at 135°C for 16 h. The solvent was evaporated. The residue, in $CHCl_3$, was filtered through Celite®. Chromatography (EtOAc / petroleum ether 1:99 \rightarrow 1:10) gave **30q** (20 mg, 9%): mp 195-196°C; 1H NMR ($CDCl_3$) δ 4.29 (3 H, s, Me), 7.62 (1 H, t, J = 8.0 Hz, Ph 5-H), 7.64 (1 H, t, J = 8.0 Hz, 7-H), 7.72 (1 H, dt, J = 7.8, 1.3 Hz, Ph 6-H), 8.38 (1 H, dt, J = 8.2, 1.2 Hz, Ph 4-H), 8.52 (1 H, dd, J = 7.8, 1.3 Hz, 6-H), 8.55 (1 H, s, 4-H), 8.56 (1 H, s, Ph 2-H), 8.65 (1 H, dt, J = 8.2, 1.1 Hz, 8-H); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 54.44 (Me), 105.90 (4-C), 113.31 (Ph 1-C), 121.03 (4a-C), 125.39 (7-C), 128.88 (6-C), 129.55 (Ph 2,5- C_2), 130.98 (Ph 6-C), 131.30 (8-C), 132.45 (Ph 4-C), 140.32 (CN), 145.67 (5-C), 160.92 (1-C).

3-(4-Cyanophenyl)-1-methoxy-5-nitroisoquinoline (30r). To **28** (151 mg, 630 μ mol) were added Pd_2dba_3 (58 mg, 63 μ mol), SPhos (58 mg, 140 μ mol), 4-cyanobenzeneboronic acid (150 mg, 1.3 mmol) and K_3PO_4 (279 mg, 1.3 mmol). Degassed PhMe (4.5 mL) was added and the mixture was stirred at 100°C for 16 h. The evaporation residue, in $CHCl_3$, was filtered. Chromatography (EtOAc / petroleum ether 1:99) gave **30r** (53 mg, 28%) as a yellow solid: mp 206-210°C; 1H NMR ($CDCl_3$) δ 4.30 (3 H, s, Me), 7.66 (1 H, t, J = 8.0 Hz, 7-H), 7.81 (2 H, d, J = 8.6 Hz, Ph 2,6- H_2), 8.32 (2 H, d, J = 8.6 Hz, Ph 3,5- H_2), 8.53 (1 H, dd, J = 7.8, 1.2 Hz, 6-H), 8.59 (1 H, s, 4-H), 8.66 (1 H, d, J = 8.2 Hz, 8-H); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 54.36 (Me), 106.64 (4-C), 112.68 (CN), 118.79 (Ph 4-C), 120.80 (8a-C), 125.56 (7-C), 127.58 (Ph 2,6- H_2), 128.85 (6-C), 129.67 (4a-C), 131.26 (8-C), 132.53 (Ph 3,5- H_2), 142.86 (3-C), 145.16 (5-C), 149.59 (Ph 1-C), 160.84 (1-C).

5-Amino-1-methoxy-3-(3-methoxyphenyl)isoquinoline (31e). Compound **30e** (40 mg, 140 μ mol) was stirred vigorously with Pd/C (10%, 44 mg) in EtOH (9 mL) under H_2 for 5 h. Filtration (Celite®) and evaporation yielded **31e** (31 mg, 81%) as a pale yellow solid: mp 146-149°C; 1H NMR ($CDCl_3$) δ 3.91 (3 H, s, Ph OMe), 4.21 (3 H, s, 1-OMe), 6.93 (2 H, m, Ph 6-H + 6-H), 7.31 (1 H, t, J = 7.8 Hz, 7-H), 7.39 (1 H, t, J = 8.0 Hz, Ph 5-H), 7.60 (1 H, s, 4-H), 7.71 (3 H, m, Ph 2,4- H_2 + 8-H); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 53.60 (1-OMe), 55.31

(Ph-OMe), 104.17 (4-C), 112.39 (Ph 2-C), 113.47 (Ph 6-C), 114.05 (6-C), 114.47 (8-C), 118.94 (Ph 4-C), 119.57 (8a-C), 126.75 (7-C), 128.36 (4a-C), 129.54 (Ph 5-C), 141.22 (Ph 1-C), 141.58 (5-C), 146.53 (3-C), 159.92 (Ph 3-C), 160.68 (1-C); MS m/z 303.1110 ($M + Na$)⁺ ($C_{17}H_{16}N_2NaO_2$ requires 303.1110), 281.1278 ($M + H$)⁺ ($C_{17}H_{17}N_2O_2$ requires 281.1290).

5-Amino-1-methoxy-3-(2-trifluoromethylphenyl)isoquinoline (31g). Compound **30g** (48 mg, 140 μ mol) was stirred vigorously with Pt/C (1%, 53 mg) in EtOH (6.0 mL) under H_2 for 4 h. Filtration (Celite®) and evaporation gave **31g** (29 mg, 66%) as a yellow solid: mp 172–174°C; 1H NMR ($CDCl_3$) δ 4.13 (OMe), 6.96 (1 H, dd, $J = 7.5, 0.5$ Hz, 6-H), 7.28 (1 H, s, 4-H), 7.37 (1 H, t, $J = 7.5$ Hz, 7-H), 7.51 (1 H, t, $J = 7.5$ Hz, Ph 5-H), 7.63 (2 H, m, Ph 4,6-H₂), 7.73 (1 H, d, $J = 8.5$ Hz, 8-H), 7.81 (1 H, d, $J = 8.0$ Hz, Ph 3-H); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 53.85 (Me), 108.10 (4-C), 114.03 (6-C), 114.32 (8-C), 119.34 (8a-C), 124.28 (q, $J = 272$ Hz, CF_3), 126.69 (q, $J = 5.1$ Hz, Ph 3-C), 127.17 (7-C), 127.57 (4a-C), 127.81 (Ph 5-C), 128.54 (q, $J = 30.1$ Hz, Ph 2-C), 131.41 (Ph 6-C), 131.90 (Ph 4-C), 140.55 (Ph 1-C), 141.56 (5-C), 147.56 (3-C), 160.35 (1-C); MS m/z 341.0872 ($M + Na$)⁺ ($C_{17}H_{13}F_3N_2NaO$ requires 341.0880).

5-Amino-1-methoxy-3-(3-trifluoromethylphenyl)isoquinoline (31h). Compound **30h** (152 mg, 440 μ mol) was stirred vigorously with Pd/C (10%, 165 mg) in EtOH (8.0 mL) under H_2 for 5.5 h. Filtration (Celite®) and evaporation gave **31h** (120 mg, 87%) as a pale buff solid: mp 89–91°C; 1H NMR ($CDCl_3$) δ 4.22 (3 H, s, Me), 6.94 (1 H, d, $J = 7.4$ Hz, 6-H), 7.33 (1 H, t, $J = 7.8$ Hz, 7-H), 7.55 (1 H, t, $J = 7.7$ Hz, Ph 5-H), 7.62 (2 H, m, 4-H + Ph 4-H), 7.70 (1 H, d, $J = 8.2$ Hz, 8-H), 8.32 (1 H, d, $J = 7.6$ Hz, Ph 6-H), 8.40 (1 H, s, Ph 2-H); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 53.70 (Me), 104.50 (4-C), 114.37 (6-C), 114.57 (8-C), 119.87 (4a-C), 123.23 (q, $J = 3.9$ Hz, Ph 2-C), 124.39 (q, $J = 270.8$ Hz, CF_3), 124.63 (q, $J = 3.9$ Hz, Ph 4-C), 127.24 (7-C), 128.22 (8a-C), 129.00 (Ph 5-C), 129.66 (Ph 6-C), 130.95 (q, $J = 31.8$ Hz, Ph 3-C), 140.44 (Ph 1-C), 141.75 (5-C), 145.16 (3-C), 160.97 (1-C); ^{19}F NMR ($CDCl_3$) δ -62.50 (s, CF_3); MS m/z 319.1048 ($M + H$)⁺ ($C_{17}H_{14}F_3N_2O$ requires 319.1060).

5-Amino-1-methoxy-3-(4-trifluoromethylphenyl)isoquinoline (31i). Compound **30i** (151 mg, 430 μ mol) was stirred vigorously with Pd/C (10%, 165 mg) in EtOH (8.0 mL) under H_2 for 5.5 h. Filtration (Celite®) and evaporation gave **31i** (120 mg, 87%) as a buff solid: mp 141–142°C; 1H NMR ($CDCl_3$) δ 4.21 (3 H, s, Me), 6.95 (1 H, dd, $J = 7.5, 0.8$ Hz, 6-H), 7.34 (1 H, t, $J = 7.7$ Hz, 7-H), 7.65 (1 H, s, 4-H), 7.71 (3 H, m, 8-H + Ph 3,5-H₂), 8.25 (2 H, d, $J = 8.2$ Hz, Ph 2,6-H₂); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 53.70 (Me), 104.97 (4-C), 114.40 (6-C), 114.58 (8-C), 119.96 (4a-C), 123.26 (q, $J = 269.9$ Hz, CF_3), 125.48 (q, $J = 3.9$ Hz, Ph 3,5-C₂), 126.68 (Ph 2,6-C₂), 127.37 (7-C), 128.16 (8a-C), 129.86 (q, $J = 31.9$ Hz, Ph 4-C), 141.78 (5-C), 143.06 (Ph 1-C), 145.21 (3-C), 160.97 (1-C); ^{19}F NMR ($CDCl_3$) δ -62.40 (s, CF_3); MS m/z 317.0907 ($M - H$)⁻ ($C_{17}H_{12}F_3N_2O$ requires 317.0900).

5-Amino-3-(4-fluorophenyl)-1-methoxyisoquinoline (31j). Compound **30j** (108 mg, 360 μ mol) was stirred vigorously with Pd/C (10%, 118 mg) in EtOH (8.0 mL) under H_2 for 6 h. Filtration (Celite®) and evaporation gave **31j** (90 mg, 69%) as an off-white solid: mp 154–155°C; 1H NMR ($CDCl_3$) δ 4.21 (3 H, s, Me), 6.94 (1 H, dd, $J = 7.5, 1.0$ Hz, 6-H), 7.15 (2 H, m, Ph 3,5-H₂), 7.31 (1 H, t, $J = 7.5$ Hz, 7-H), 7.54 (1 H, s, 4-H), 7.69 (1 H, dt, $J = 8.2, 1.0$ Hz, 8-H), 8.13 (2 H, m, Ph 2,6-H₂); ^{13}C NMR ($CDCl_3$) (HSQC / HMBC) δ 53.62 (Me), 103.64 (4-C), 114.31 (6-C), 114.67 (8-C), 115.42 (d, $J = 21.5$ Hz, Ph 3,5-C₂), 119.40 (4a-C), 126.72 (7-C), 128.62 (d, $J = 10.4$ Hz, Ph 2,6-C₂), 128.53 (8a-C), 135.85 (d, $J = 3.3$ Hz, Ph 1-C), 141.37 (5-C), 145.98 (3-C), 160.82 (1-C), 163.04 (d, $J = 246.0$ Hz, Ph 4-C); MS m/z 269.1074 ($M +$

H)⁺ (C₁₆H₁₄FN₂O requires 269.1092); ¹⁹F NMR (CDCl₃) δ -114.31 (m, F); MS *m/z* 267.0925 (M - H)⁻ (C₁₆H₁₂FN₂O requires 267.0932).

5-Amino-3-(2-chlorophenyl)-1-methoxyisoquinoline (31k). Compound **30k** (75 mg, 240 μmol) was stirred vigorously with Pt/C (1%, 84 mg) in EtOH (6.0 mL) under H₂ for 5 h. Filtration (Celite[®]) and evaporation gave **31k** (70 mg, 100%) as a yellow solid: mp 102-103 °C; ¹H NMR (CDCl₃) δ 4.18 (Me), 6.93 (1 H, dd, *J* = 7.5 Hz, 6-H), 7.35 (3 H, m, 7-H + Ph 4,5-H₂), 7.51 (1 H, dd, *J* = 8.0, 1.0 Hz, Ph 3-H), 7.56 (1 H, s, 4-H), 7.73 (1 H, d, *J* = 8.0 Hz, 8-H), 7.76 (1 H, dd, *J* = 7.5, 1.5 Hz, Ph 6-H); ¹³C NMR (CDCl₃) (HSQC / HMBC) δ 53.78 (Me), 109.13 (4-C), 113.89 (6-C), 114.14 (8-C), 119.29 (4a-C), 126.75 (Ph 4-C), 127.17 (7-C), 127.59 (8a-C), 128.83 (Ph 5-C), 130.27 (Ph 3-C), 131.75 (Ph 6-C), 132.32 (Ph 1-C), 139.34 (Ph 2-C), 141.65 (5-C), 145.86 (3-C), 160.57 (1-C); MS *m/z* 285.0803 (M + H)⁺ (C₁₆H₁₄³⁵ClN₂O requires 285.0796).

5-Amino-3-(3-chlorophenyl)-1-methoxyisoquinoline (31l). Compound **30l** (75 mg, 240 μmol) was stirred vigorously with Pt/C (1%, 84 mg) in EtOH (6.0 mL) under H₂ for 5 h. Filtration (Celite[®]) and evaporation gave **31l** (62 mg, 91%) as a yellow solid: mp 94-95°C; ¹H NMR (CDCl₃) 4.20 (Me), 6.93 (1 H, dd, *J* = 7.5, 0.5 Hz, 6-H), 7.33 (3 H, m, 7-H + Ph 5,6-H₂), 7.57 (1 H, s, 4-H), 7.69 (1 H, d, *J* = 8.5 Hz, 8-H), 8.01 (1 H, d, *J* = 7.5 Hz, Ph 3-H), 8.14 (1 H, s, Ph 2-H); ¹³C NMR (CDCl₃) (HSQC / HMBC) 53.69 (Me), 104.39 (4-C), 114.31 (6-C), 114.53 (8-C), 119.72 (4a-C), 124.47 (Ph 4-C), 126.57 (Ph 2-C), 127.07 (7-C), 128.19 (8a-C), 128.01 (Ph 5-C), 129.74 (Ph 6-C), 134.56 (Ph 3-C), 141.47 (5-C), 141.57 (Ph 1-C), 145.18 (3-C), 160.78 (1-C); MS *m/z* 285.0793 (M + H)⁺ (C₁₆H₁₄³⁵ClN₂O requires 285.0796).

5-Amino-3-(2,6-dichlorophenyl)-1-methoxyisoquinoline (31n). Compound **30n** (30 mg, 90 μmol) was stirred vigorously with Pd/C (10%, 33 mg) in EtOH (5.0 mL) under H₂ for 5 h. Filtration (Celite[®]) and evaporation gave **31n** (27 mg, 94%) as a pale orange solid: mp 103-104°C; ¹H NMR (CDCl₃) δ 4.12 (3 H, s, Me), 6.95 (1 H, dd, *J* = 7.5, 1.0 Hz, 6-H), 7.19 (1 H, d, *J* = 0.9 Hz, 4-H), 7.25 (1 H, t, *J* = 8.6 Hz, Ph 4-H), 7.36 (1 H, t, *J* = 7.6 Hz, 7-H), 7.42 (2 H, d, *J* = 8.3 Hz, Ph 3,5-H₂), 7.74 (1 H, dt, *J* = 8.2, 1.0 Hz, 8-H); ¹³C NMR (CDCl₃) (HSQC / HMBC) δ 54.02 (Me), 109.70 (4-C), 114.00 (6-C), 114.37 (8-C), 127.36 (7-C), 128.15 (Ph 3,5-C₂), 129.30 (Ph 4-C), 119.69 (4a-C), 127.62 (8a-C), 135.25 (Ph 2,6-C₂), 138.92 (Ph 1-C), 141.65 (5-C), 144.58 (3-C), 160.94 (1-C); MS *m/z* 321.0356 (M + H)⁺ (C₁₆H₁₃³⁵Cl³⁷ClN₂O requires 321.0375), 319.0387 (M + H)⁺ (C₁₆H₁₃³⁵Cl₂N₂O requires 319.0405).

5-Amino-3-(4-hydroxyphenyl)-1-methoxyisoquinoline (31p). Compound **30p** (65 mg, 220 μmol) was stirred vigorously with Pd/C (10%, 71.5 mg) in EtOH (5.0 mL) under H₂ for 6 h. Filtration (Celite[®]) and evaporation gave **31p** (63 mg, 98%) as a yellow solid: mp >230°C; ¹H NMR (CD₃OD) δ 4.17 (3 H, s, Me), 6.87 (2 H, d, *J* = 7.0 Hz, Ph 3,5-H₂), 6.94 (1 H, d, *J* = 7.0 Hz, 6-H), 7.22 (1 H, t, *J* = 8.0 Hz, 7-H), 7.53 (1 H, d, *J* = 8.5 Hz, 8-H), 7.81 (1 H, s, 4-H), 8.07 (2 H, d, *J* = 7.0 Hz, Ph 2,6-H₂); ¹³C NMR (CD₃OD) (HSQC / HMBC) δ 53.84 (Me), 104.35 (4-C), 114.14 (8-C), 114.63 (6-C), 116.24 (Ph 3,5-C₂), 120.52 (4a-C), 127.40 (7-C), 128.85 (Ph 2,6-C₂), 130.19 (8a-C), 132.74 (Ph 1-C), 144.38 (5-C), 147.73 (3-C), 158.86 (Ph 4-C), 161.74 (1-C); MS *m/z* 267.1123 (M + H)⁺ (C₁₆H₁₅N₂O₂ requires 267.1135).

5-Amino-3-(3-cyanophenyl)-1-methoxyisoquinoline (31q). Compound **30q** (34 mg, 110 μmol) was stirred vigorously with Pd/C (10%, 38 mg) in EtOH (5.0 mL) under H₂ for 6.5 h. Filtration (Celite[®]), evaporation and chromatography (ethyl acetate / petroleum ether 1:39 → 1:4) gave **31q** (11.2 mg, 37%) as a golden buff solid: mp 183-184°C; ¹H NMR (CDCl₃) δ 4.22 (3 H, s, Me), 6.96 (1 H, dd, *J* = 7.5, 1.0 Hz, 6-H), 7.35 (1 H, t, *J* = 7.6 Hz, 7-H), 7.56 (1

H, t, $J = 7.4$ Hz, Ph 5-H), 7.62 (1 H, s, 4-H), 7.63 (1 H, dt, $J = 7.9, 1.5$ Hz, Ph 6-H), 7.70 (1 H, dt, $J = 8.2, 0.9$ Hz, 8-H), 8.36 (1 H, dt, $J = 7.9, 1.3$ Hz, Ph 4-H), 8.46 (1 H, t, $J = 1.3$ Hz, Ph 2-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 53.80 (Me), 104.72 (4-C), 112.74 (Ph 3-C), 114.52 (6-C), 114.58 (8-C), 119.14 (CN), 120.03 (8a-C), 127.53 (7-C), 128.08 (4a-C), 129.31 (Ph 5-C), 130.26 (Ph 2-C), 130.49 (Ph 4-C), 131.27 (Ph 6-C), 140.84 (Ph 1-C), 141.81 (5-C), 144.22 (3-C), 161.09 (1-C); MS m/z 276.1128 ($\text{M} + \text{H}$) $^+$ ($\text{C}_{17}\text{H}_{14}\text{N}_3\text{O}$ requires 276.1137).

5-Amino-3-(4-cyanophenyl)-1-methoxyisoquinoline (31r). Compound **30r** (37 mg, 120 μmol) was stirred vigorously with Pd/C (10%, 41 mg) in EtOH (5.5 mL) under H_2 for 6.5 h. Filtration (Celite[®]), evaporation and chromatography (EtOAc / petroleum ether 1:39 \rightarrow 1:4) gave **31r** (17.3 mg, 52%) as an amber-coloured solid: mp 203-204 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 4.21 (3 H, s, Me), 6.96 (1 H, dd, $J = 7.6, 1.0$ Hz, 6-H), 7.36 (1 H, t, $J = 7.6$ Hz, 7-H), 7.67 (1 H, s, 4-H), 7.70 (1 H, dt, $J = 7.3, 0.9$ Hz, 8-H), 7.74 (2 H, d, $J = 8.7$ Hz, Ph 3,5- H_2), 8.25 (2 H, d, $J = 8.7$ Hz, Ph 2,6- H_2); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 53.76 (Me), 105.55 (4-C), 111.27 (Ph 4-C), 114.58 (6-C), 114.61 (8-C), 119.17 (CN), 120.18 (4a-C), 126.89 (Ph 2,6- C_2), 127.77 (7-C), 127.98 (8a-C), 132.39 (Ph 3,5- C_2), 141.93 (5-C), 143.93 (Ph 1-C), 144.45 (3-C), 161.04 (1-C); MS m/z 276.1124 ($\text{M} + \text{H}$) $^+$ ($\text{C}_{17}\text{H}_{14}\text{N}_3\text{O}$ requires 276.1137).

Isoquinoline-1,3-dione (33). 2-Carboxyphenylacetic acid **32** (20.0 g, 111 mmol) was heated with finely ground urea (7.33 g, 122 mmol) at 175-185 $^\circ\text{C}$ for 2 h. Cooling and recrystallisation (MeOH) gave **33** (12.0 g, 67%) as an off-white solid: mp 220-222 $^\circ\text{C}$ (lit.³ mp 236-238 $^\circ\text{C}$); ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 4.09 (3 H, s, CH_2), 7.44 (1 H, d, $J = 7.6$ Hz, 5-H), 7.51 (1 H, t, $J = 7.6$ Hz, 7-H), 7.70 (1 H, td, $J = 7.6, 1.2$ Hz, 6-H), 8.07 (1 H, dd, $J = 7.8, 1.1$ Hz, 8-H), 11.36 (1 H, s, N-H); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 35.92 (4-C), 124.95 (8a-C), 127.16 (7-C), 127.41 (8-C), 127.87 (5-C), 133.47 (6-C), 136.66 (4a-C), 165.34 (1-C), 170.99 (3-C).

1,3-Dibromoisquinoline (34). Method A. PBr_3 (10 mL) was added slowly to **33** (1.41 g, 8.7 mmol) and the mixture was heated at reflux for 16 h. The evaporation residue was quenched (sat. aq. NaHCO_3) and extracted thrice with CHCl_3 . Chromatography (EtOAc / petroleum ether 3:17), followed by chromatography (EtOAc / petroleum ether 1:49) gave **34** (358 mg, 14%) as white crystals: mp 148-150 $^\circ\text{C}$ (lit.⁴ mp 147-147.5 $^\circ\text{C}$); ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 7.93 (1 H, td, $J = 6.9, 1.3$ Hz, 6-H), 8.00 (1 H, td, $J = 6.9, 1.2$ Hz, 7-H), 8.10 (1 H, dt, $J = 8.1, 0.6$ Hz, 5-H), 8.27 (1 H, d, $J = 8.4$ Hz, 8-H), 8.38 (1 H, s, 4-H); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 124.66 (4-C), 126.85 (5-C), 127.13 (8a-C), 127.68 (4a-C), 127.89 (8-C), 130.69 (6-C), 132.69 (7-C), 138.74 (3-C), 143.18 (1-C). Further elution gave **35** (66 mg, 4%) as white crystals: mp 61-63 $^\circ\text{C}$ (lit.⁴ mp 63-64 $^\circ\text{C}$); ^1H NMR ($(\text{CD}_3)_2\text{SO}$) (NOE) δ 7.80 (1 H, td, $J = 8.0, 1.2$ Hz, 6-H), 7.90 (1 H, dt, $J = 8.3, 1.2$ Hz, 7-H), 8.03 (1 H, d, $J = 8.3$ Hz, 5-H), 8.23 (1 H, d, $J = 8.3$ Hz, 8-H), 8.27 (1 H, s, 4-H), 9.24 (1 H, s, 1-H); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 123.53 (4-C), 125.76 (5-C), 127.25 (4a-C), 127.80 (8-C), 128.13 (6-C), 131.68 (7-C), 135.19 (3-C), 137.46 (8a-C), 153.19 (1-C).

1,3-Dibromoisquinoline (34). Method B. Isoquinoline-1,3-dione **33** (3.00 g, 18.6 mmol) was heated under reflux with POBr_3 (10.7 g, 37 mmol) in 1,4-dioxane (20 mL) for 22 h. The mixture was quenched with MeOH, then water. The mixture, in water, was extracted thrice with CH_2Cl_2 . Drying, evaporation and recrystallisation (PhMe) gave **34** (1.87 g, 35%) as an off-white solid, with properties as above.

4-Phenylethynylbenzonitrile (43). $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (96.5 mg, 140 μmol), CuI (52 mg, 300 μmol), sodium ascorbate (33 mg, 160 μmol) and 4-bromobenzonitrile **42** (500 mg, 2.75 mmol) were mixed in a dry flask. Degassed THF (10 mL) and dry Pr_2NH (5.0 mL) were added and the mixture was stirred at 50 °C for 30 min. Phenylethyne (281 mg, 2.75 mmol) was added and the mixture was stirred for 16 h at 50 °C. The mixture was filtered through Celite®. Evaporation and chromatography (ethyl acetate / petroleum ether 1:199 \rightarrow 1:99) gave **43** (394 mg, 70%) as an off-white solid: mp 78-79°C (lit.⁵ mp 91-92°C); ^1H NMR (CDCl_3) δ 7.38 (3 H, m, Ph 3,4,5- H_3), 7.55 (2 H, m, Ph 2,6- H_2), 7.60 (4 H, m, NCPh 2,3,5,6- H_4); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 87.66 (ethyne 1-C), 93.69 (ethyne 2-C), 111.34 (CN), 118.42 (NCPh 1-C), 122.11 (Ph 1-C), 128.11 (NCPh 4-C), 128.42 (Ph 3,5- C_2), 129.04 (Ph 4-C), 131.69 (Ph 2,6- C_2), 131.93 (NCPh 2,6- C_2), 131.95 (NCPh 3,5- C_2).

4-Dimethylaminomethylbenzonitrile (45a). 4-Bromomethylbenzonitrile (1.00 g, 5.1 mmol) was stirred with aq. Me_2NH (40%, 4.0 mL) for 16 h. The mixture was diluted with water and extracted with CH_2Cl_2 . The extract was washed with aqueous citric acid (10%). The combined aqueous solutions were basified by addition of aq. NaOH (15%) and extracted with CH_2Cl_2 . The combined solutions in CH_2Cl_2 were dried and the solvent was evaporated to give **45a** (420 mg, 51%) as a colourless oil (lit.⁶ oil): ^1H NMR (CDCl_3) δ 2.24 (6 H, s, NMe_2), 3.47 (2 H, s, CH_2), 7.43 (2 H, d, $J = 8.2$ Hz, 3,5- H_2), 7.61 (2 H, d, $J = 8.2$ Hz, 2,6- H_2); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 45.42 (NMe_2), 63.83 (CH_2), 110.92 (1-C), 118.95 (CN), 129.51 (3,5- C_2), 132.13 (2,6- C_2), 144.62 (4-C).

4-(Piperidin-1-ylmethyl)benzonitrile (45b). 4-Bromomethylbenzonitrile (500 mg, 2.6 mmol) was stirred with K_2CO_3 (388 mg, 2.8 mmol) and piperidine (238 mg, 2.8 mmol) in dry DMF (6.0 mL) at 20°C for 3 h, then at 90°C for 3 d. The mixture was then cooled to 20°C. Water (18 mL) was added and the mixture was stirred for 30 min. This mixture was diluted with EtOAc. The suspension was washed thrice with brine and dried. Evaporation of the solvent gave **45b** (340 mg, 67%) as a pale orange oil (lit.⁷ oil): ^1H NMR (CDCl_3) δ 1.44 (2 H, m, piperidine 4- H_2), 1.57 (4 H, m, piperidine 3,5- H_4), 2.36 (4 H, m, piperidine 2,6- H_4), 3.50 (2 H, s, PhCH_2), 7.44 (2 H, d, $J = 8.0$ Hz, Ph 3,5- H_2), 7.59 (2 H, d, $J = 8.3$ Hz, Ph 2,6- H_2); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 24.20 (piperidine 4-C), 25.94 (piperidine 3,5- C_2), 54.60 (piperidine 2,6- C_2), 63.25 (PhCH_2), 110.58 (Ph 1-C), 119.07 (CN), 129.46 (Ph 3,5- C_2), 131.99 (Ph 2,6- C_2), 144.84 (Ph 4-C).

4-(Pyrrolidin-1-ylmethyl)benzonitrile (45c). 4-Bromomethylbenzonitrile (1.00 g, 5.1 mmol) in dry THF (15 mL) was stirred with Et_3N (1.08 g, 10.7 mmol) and pyrrolidine (760 mg, 10.7 mmol) for 2 d. This mixture was diluted with EtOAc, washed thrice with water and dried. Evaporation of the solvent gave **45c** (935 mg, 98%) as a pale orange oil (lit.⁸ oil): ^1H NMR (CDCl_3) δ 1.79 (4 H, m, pyrrolidine 2,3- H_4), 2.50 (4 H, m, pyrrolidine 1,4- H_4), 3.65 (2 H, s, PhCH_2), 7.44 (2 H, d, $J = 8.5$ Hz, Ph 3,5- H_2), 7.59 (2 H, d, $J = 8.4$ Hz, Ph 2,6- H_2); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 23.53 (pyrrolidine 2,3- C_2), 54.24 (pyrrolidine 1,4- C_2), 60.23 (PhCH_2), 110.67 (Ph 1-C), 119.05 (CN), 129.29 (Ph 3,5- C_2), 132.10 (Ph 2,6- C_2), 145.29 (Ph 4-C).

4-((4-Methylpiperazin-1-yl)methyl)benzonitrile (45d). 4-Bromomethylbenzonitrile (1.0 g, 5.1 mmol) was stirred for 24 h with Et_3N (1.03 g, 10.2 mmol) and 1-methylpiperazine (760 mg, 7.6 mmol) in dry CH_2Cl_2 (10 mL). This mixture was diluted with CH_2Cl_2 and washed thrice with sat. aq. NaHCO_3 and H_2O . Drying and evaporation gave **45d** (650 mg, 59%) as a white solid: mp 65-67°C (lit.⁹ mp 62-64°C): ^1H NMR (CDCl_3) δ 2.29 (3 H, s, Me), 2.47 (8 H, m, piperazine 2,3,5,6- H_8), 3.54 (2 H, s, PhCH_2), 7.43 (2 H, d, $J = 8.2$ Hz, Ph 3,5- H_2), 7.58 (2

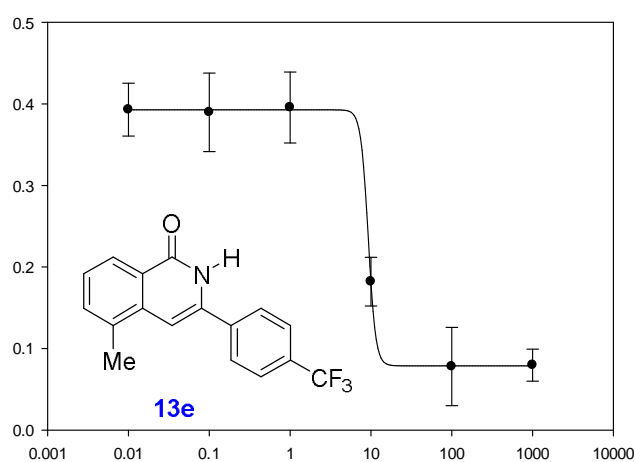
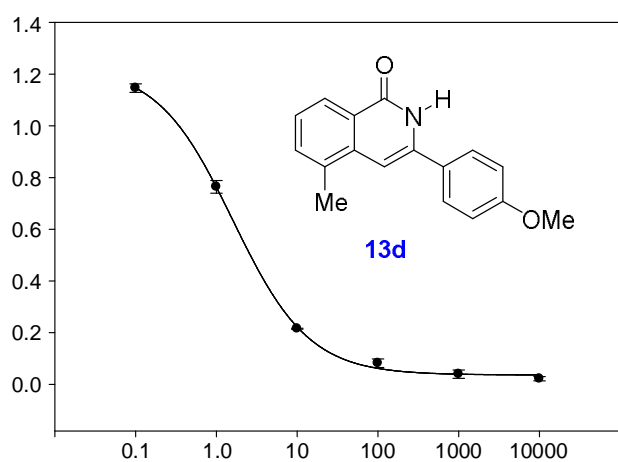
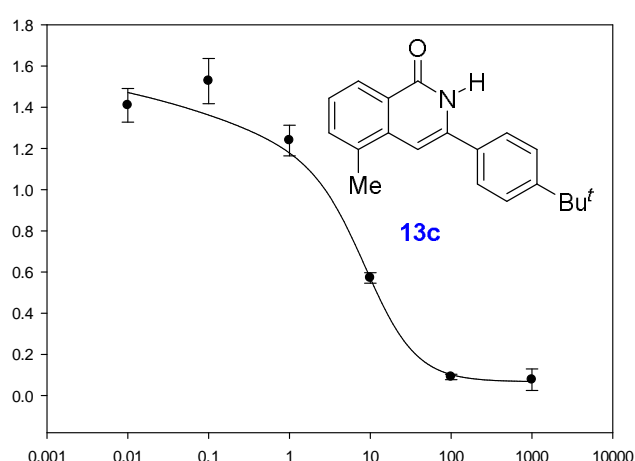
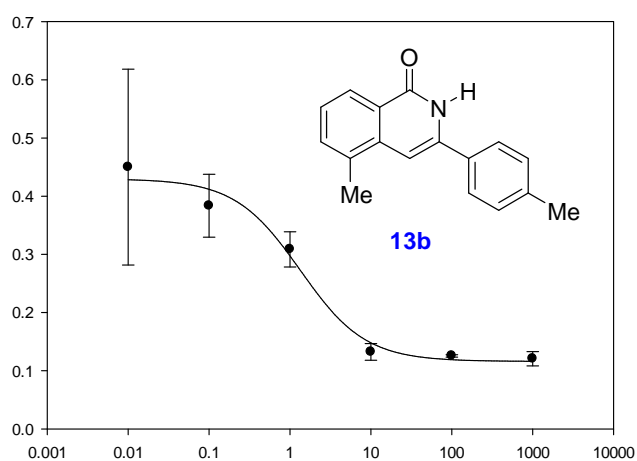
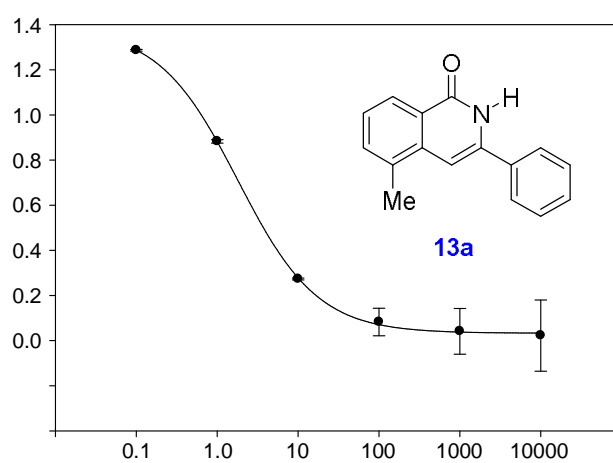
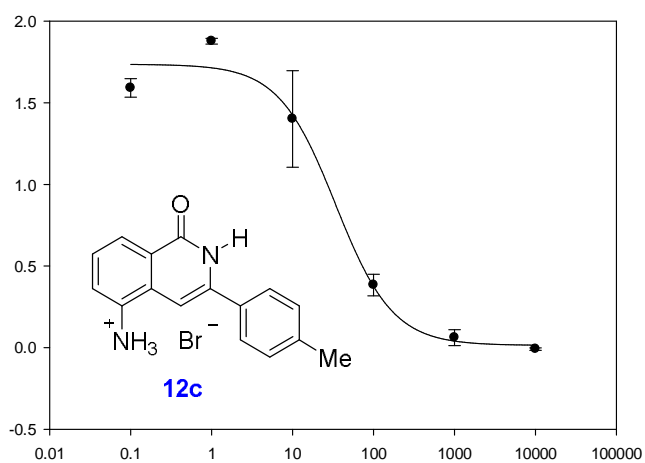
H, d, $J = 8.2$ Hz, Ph 2,6- H_2); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 45.98 (Me), 53.08 (piperazine 2,6- C_2), 55.05 (piperazine 3,5- C_2), 62.38 (Ph CH_2), 110.85 (Ph 1- C), 118.97 (CN), 129.49 (Ph 3,5- C_2), 132.10 (Ph 2,6- C_2), 144.23 (Ph 4- C).

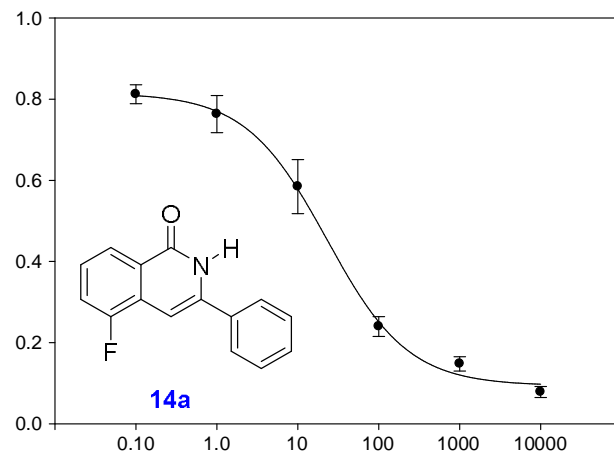
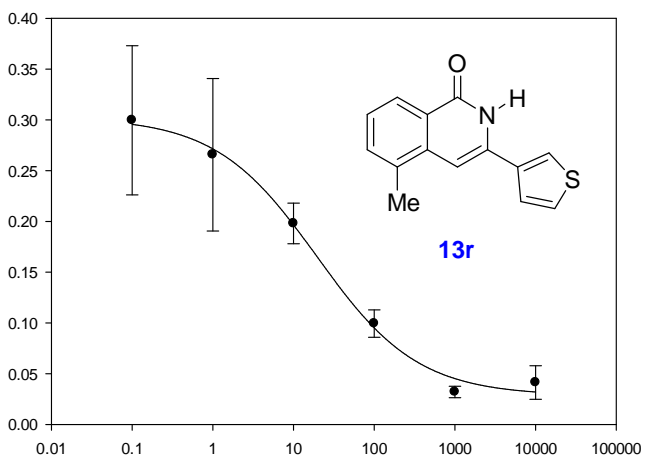
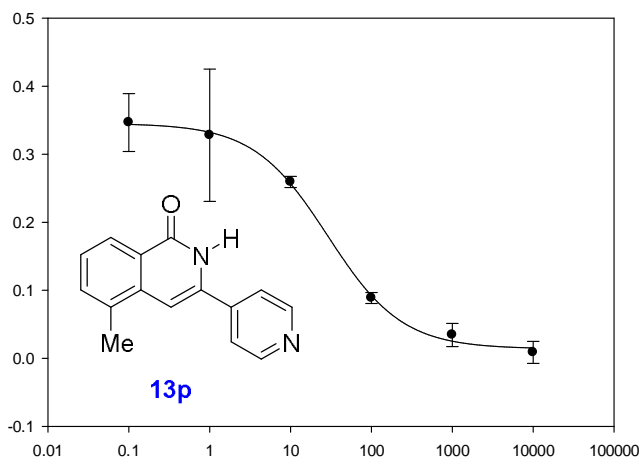
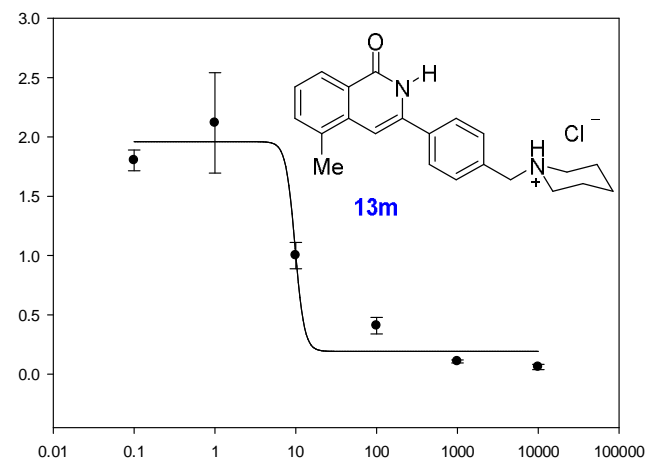
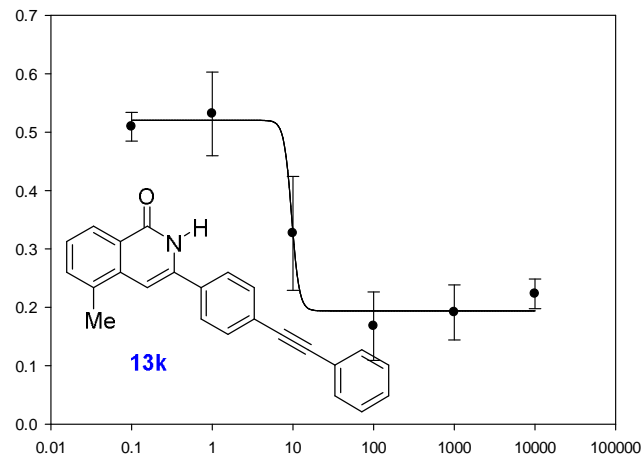
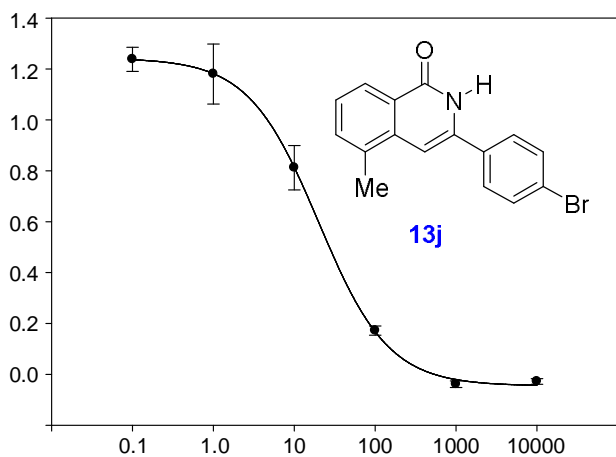
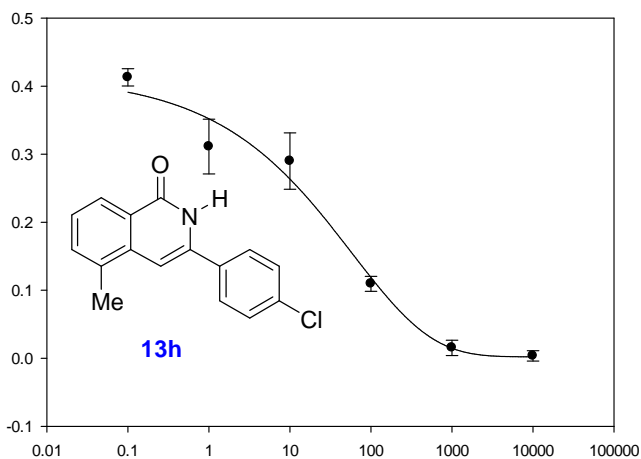
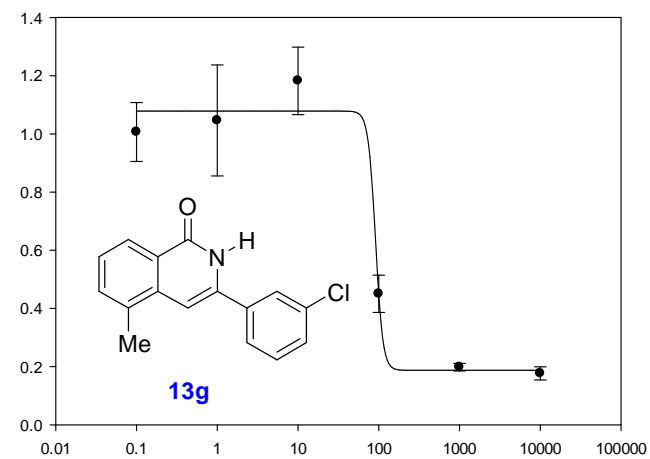
Ferrocenenitrile (47). Ferrocenecarboxylic acid **46** (500 mg, 2.2 mmol) was stirred with oxalyl chloride (634 mg, 5.0 mmol) for 1 h. The evaporation residue, in dry THF (5.0 mL), was added dropwise to saturated NH_3 in Et_2O (25 mL). After 15 min, H_2O (20 mL) was added and organic layer was washed thrice (H_2O). Drying and evaporation gave ferrocenecarboxamide (370 mg, 74%) as a pale orange solid: mp 168-169°C (lit.¹⁰ mp 168-171°C); ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 4.15 (5 H, s, Fc'- H_5), 4.32 (2 H, br, Fc 3,4- H_2), 4.74 (2 H, br, Fc 2,5- H_2), 6.91 (1 H, br, NH), 7.28 (1 H, br, NH); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 68.49 (Fc 2,5- C_2), 69.31 (Fc'- C_5), 69.91 (Fc 3,4- C_2), 76.42 (Fc 1- C), 171.01 (C=O). This material (352 mg, 1.5 mmol) was stirred with POCl_3 (3.5 mL) at 120°C for 2 h, followed by cooling to 0°C and quench with H_2O (1.0 mL). The mixture was diluted with EtOAc and washed thrice with H_2O . Drying and evaporation gave **47** (360 mg, 99%) as a dark orange solid: mp 105-107°C (lit.¹¹ mp 106-106.5°C); ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 4.34 (5 H, s, Fc'- H_5), 4.50 (2 H, s, Fc 3,4- H_2), 4.83 (2 H, s, Fc 2,5- H_2); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) (HSQC / HMBC) δ 51.05 (Fc 1- C), 70.32 (Fc'- C_5), 71.00 (Fc 3,4- C_2), 71.61 (Fc 2,5- C_2), 120.21 (CN).

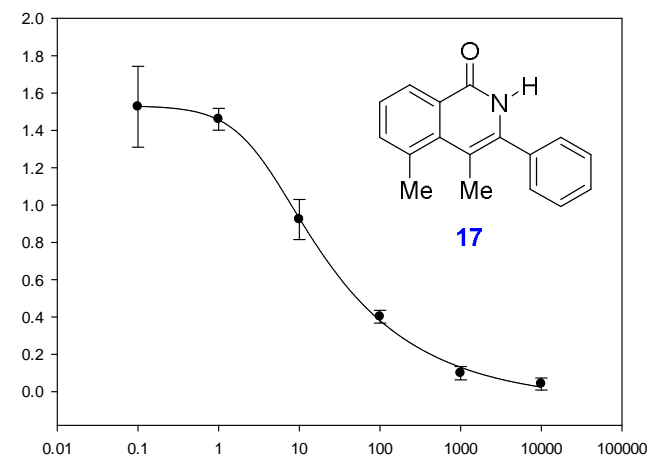
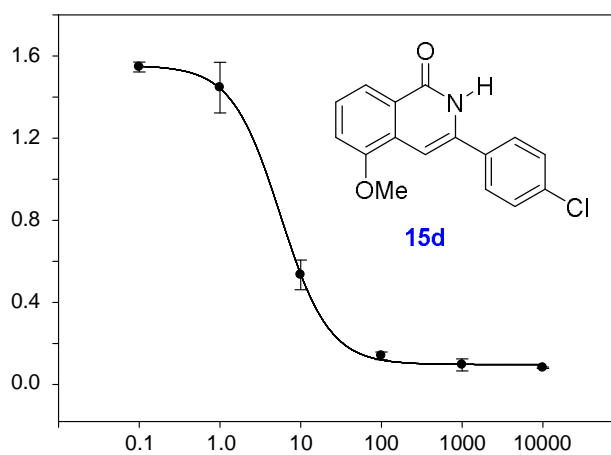
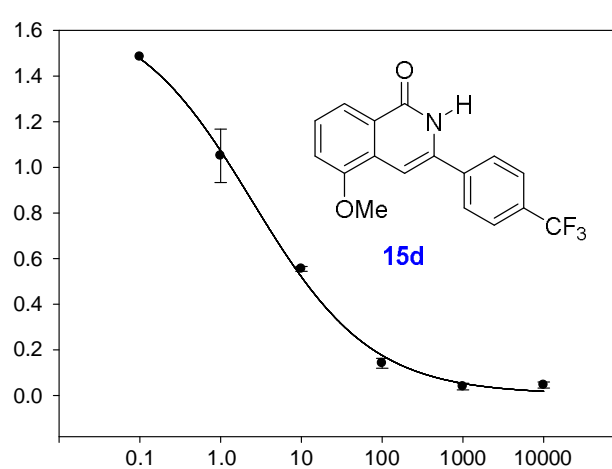
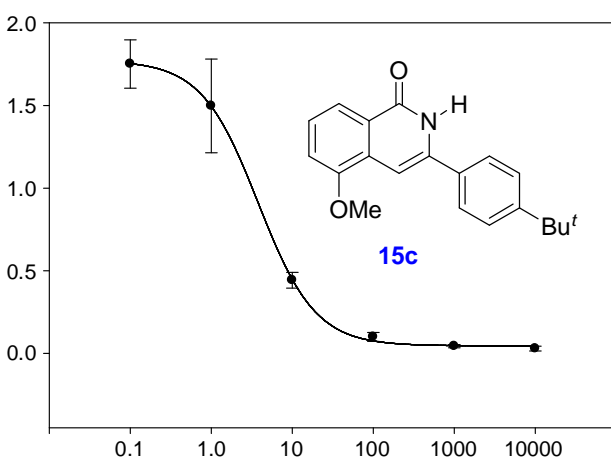
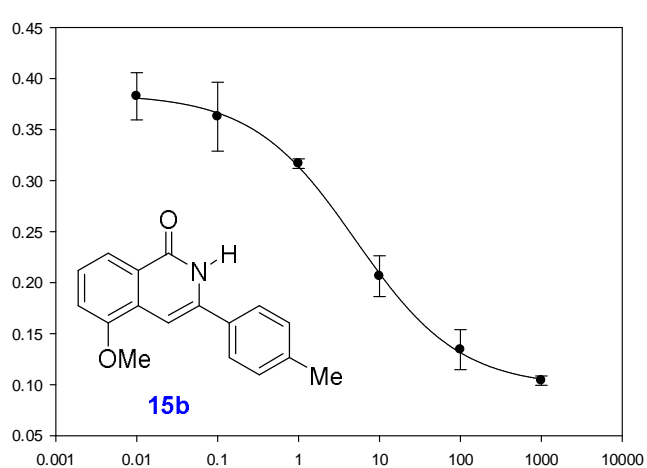
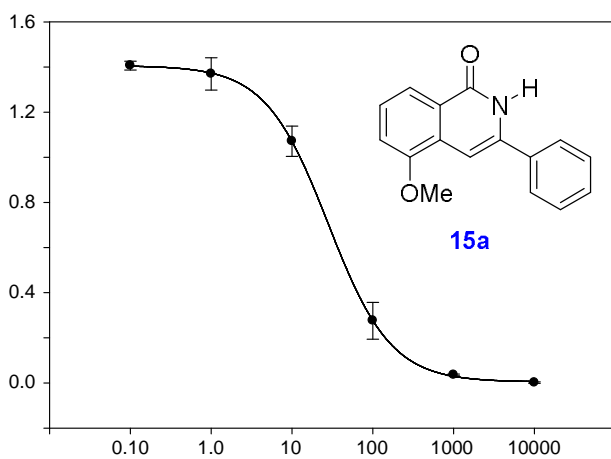
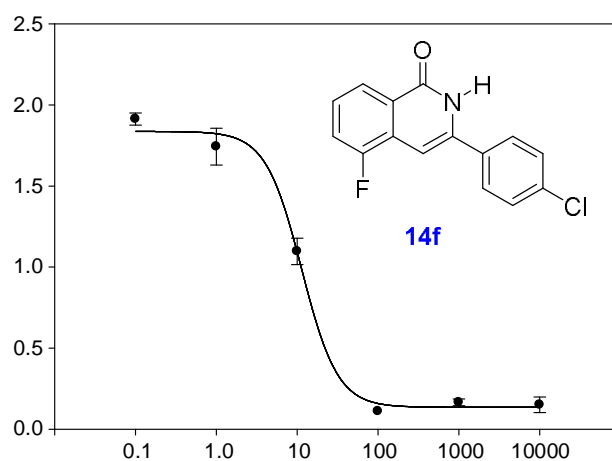
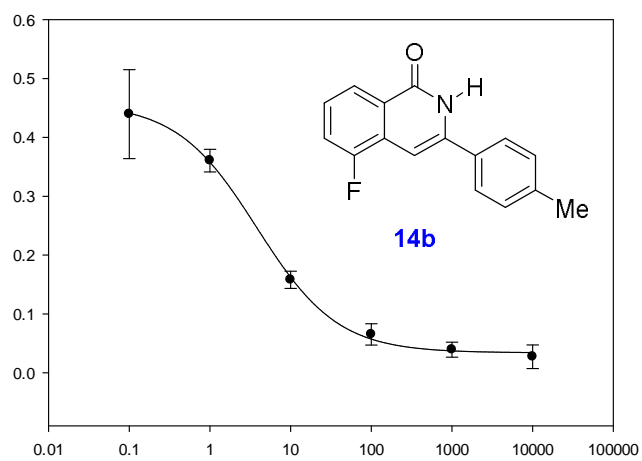
3-Fluoro-2,N,N-trimethylbenzamide (49). SOCl_2 (3.0 g, 25 mmol) was added to **48** (1.00 g, 6.5 mmol) at 0°C. The mixture was heated at reflux for 16 h, then the excess SOCl_2 was evaporated. The residue, in CH_2Cl_2 (1.0 mL), was added dropwise to a stirred solution of Me_2NH in water (40 %, 3.7 mL) at 10°C. The mixture was then stirred at 20°C for 2.5 h. The mixture was diluted with CH_2Cl_2 , then washed thrice with water and dried. Evaporation gave **49** (1.00 g, 85%) as a pale orange oil: ^1H NMR (CDCl_3) δ 2.19 (3 H, d, $J = 2.0$ Hz, 2-Me), 2.82 (3 H, s, N-Me), 3.13 (3 H, s, N-Me), 6.96 (1 H, d, $J = 7.6$ Hz, 6-H), 7.01 (1 H, ddd, $J = 7.4, 6.1, 0.8$ Hz, 4-H), 7.18 (1 H, m, 5-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 11.20 (d, $J = 4.5$ Hz, 2-Me), 34.54 (N-Me), 38.28 (N-Me), 115.31 (d, $J = 22.5$ Hz, 4-C), 121.39 (d, $J = 3.6$ Hz, 6-C), 121.59 (d, $J = 18.3$ Hz, 2-C), 127.45 (d, $J = 8.6$ Hz, 5-C), 138.90 (d, $J = 3.9$ Hz, 1-C), 161.25 (d, $J = 244.5$ Hz, 3-C), 169.98 (d, $J = 3.3$ Hz, C=O); ^{19}F NMR (CDCl_3) δ -115.66 (d, $J = 6.1$ Hz, 3-F); MS m/z ($M + H$)⁺ 182.0973 ($\text{C}_{10}\text{H}_{13}\text{FNO}$ requires 182.0976).

3-Methoxy-2,N,N-trimethylbenzamide (51). SOCl_2 (2.74 g, 23 mmol) was added to **50** (1.00 g, 6.0 mmol) at 0°C. The mixture was heated at reflux for 16 h, then the excess SOCl_2 was evaporated. The residue, in CH_2Cl_2 (3.0 mL), was added dropwise to a stirred solution of Me_2NH in water (40 %, 3.7 mL) at 10°C. The mixture was then stirred at 20°C for 3.5 h. The mixture was diluted with CH_2Cl_2 , then washed thrice with water and dried. The solvent was evaporated to give **51** (980 mg, 85%) as a pale yellow oil: ^1H NMR (CDCl_3) δ 2.12 (3 H, s, 2-Me), 2.81 (3 H, s, N-Me), 3.12 (3 H, s, N-Me), 3.82 (3 H, s, OMe), 6.76 (1 H, dd, $J = 7.6, 0.8$ Hz, 4-H), 6.81 (1 H, d, $J = 8.2$ Hz, 6-H), 7.18 (1 H, t, $J = 7.6$ Hz, 5-H); ^{13}C NMR (CDCl_3) (HSQC / HMBC) δ 12.42 (Me), 34.44 (N-Me), 38.24 (N-Me), 55.44 (OMe), 110.10 (6-C), 117.73 (4-C), 122.69 (2-C), 126.97 (5-C), 137.99 (1-C), 157.76 (3-C), 171.23 (C=O); MS m/z ($M + \text{Na}$)⁺ ($\text{C}_{11}\text{H}_{15}\text{NNaO}_2$ requires 216.0995).

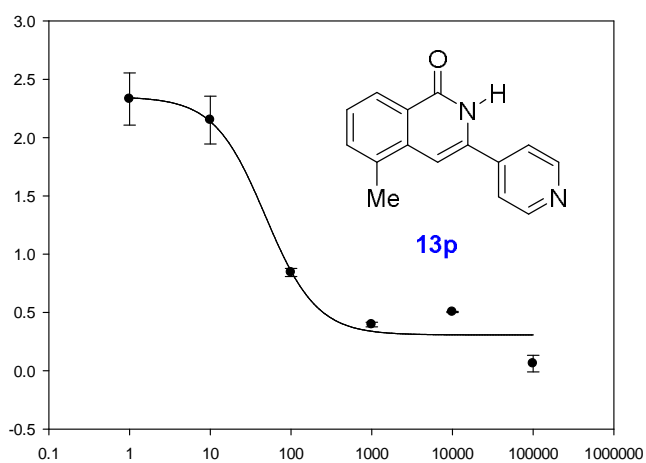
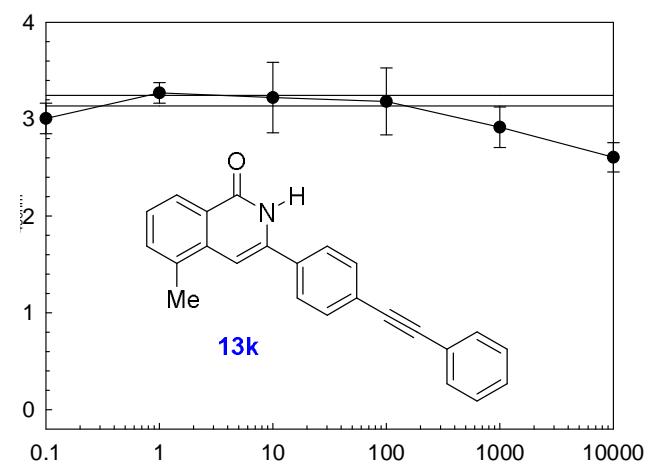
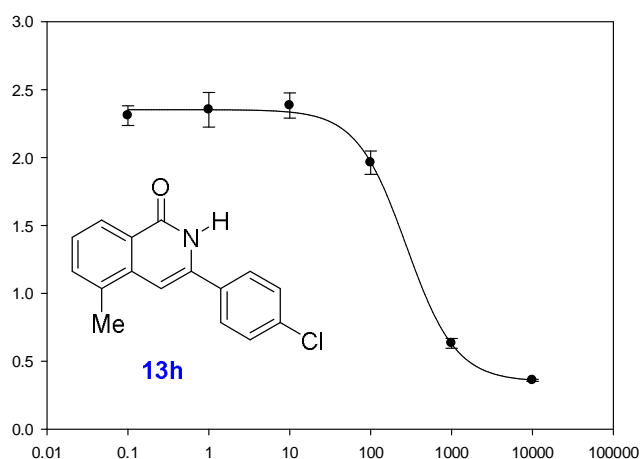
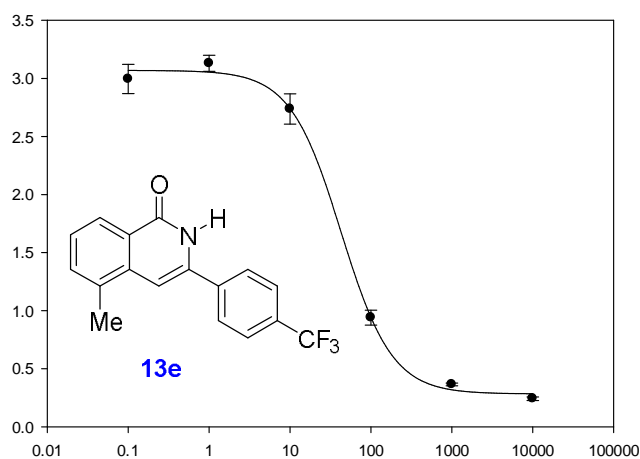
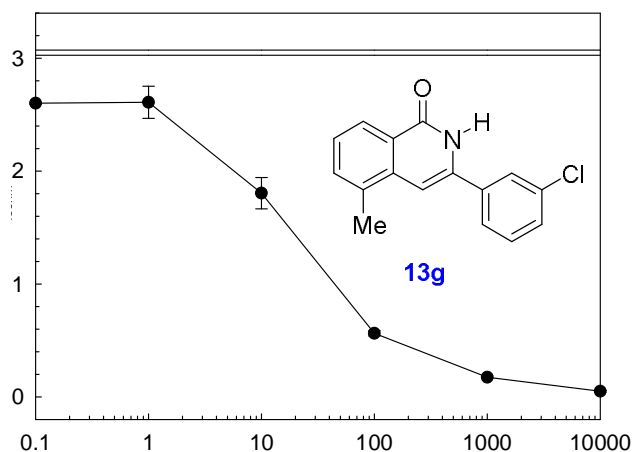
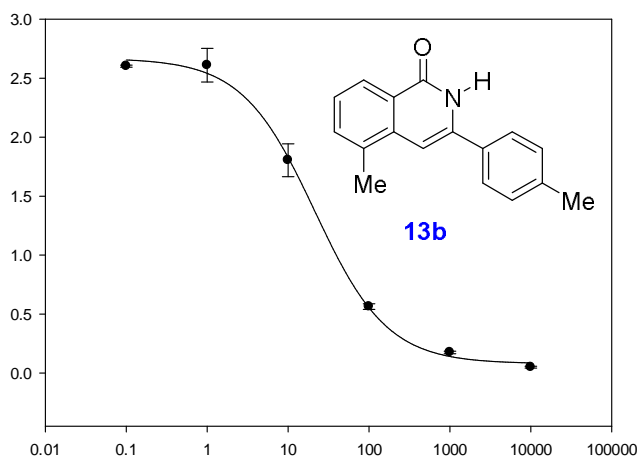
Section C: Examples of graphs of enzyme activity vs. concentration for inhibition of tankyrase-2 by isoquinolin-1-ones. X-Axes – concentration of inhibitor (nM); Y-axes – optical density (490 nm).

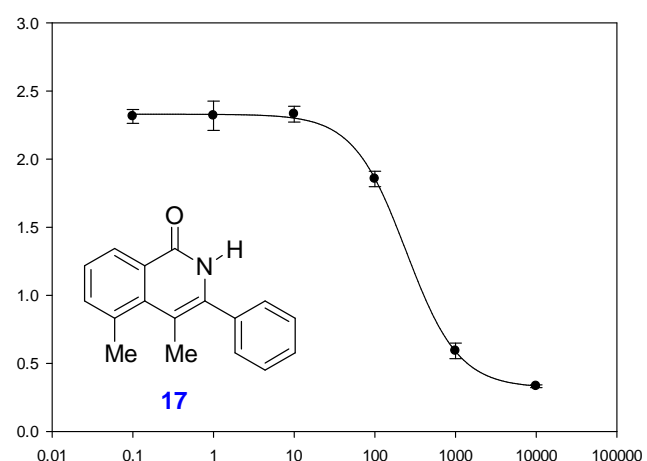
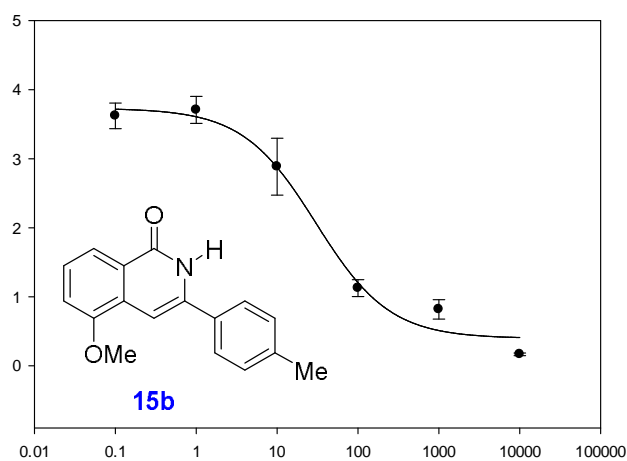
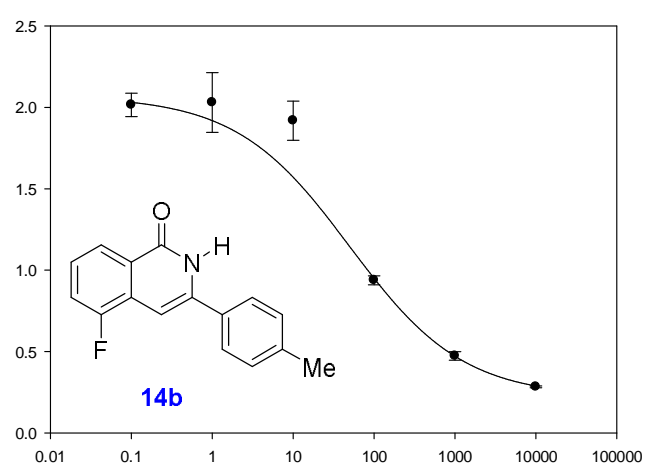
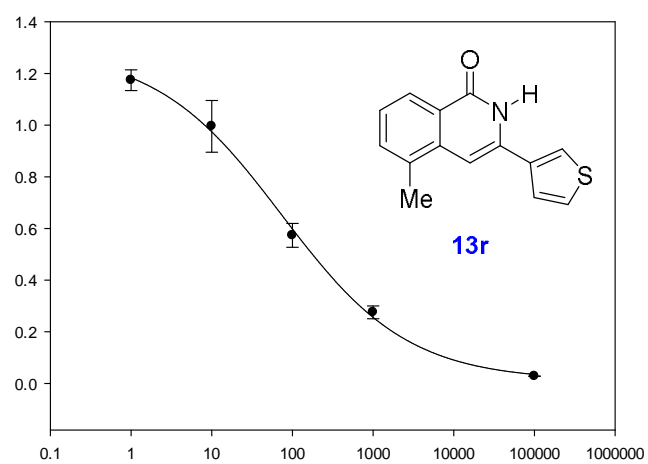




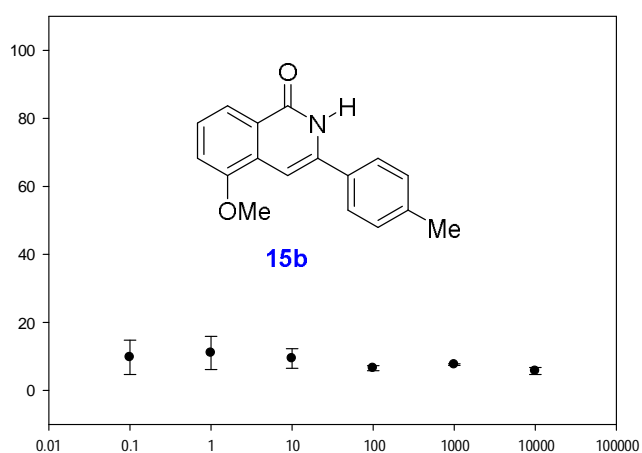
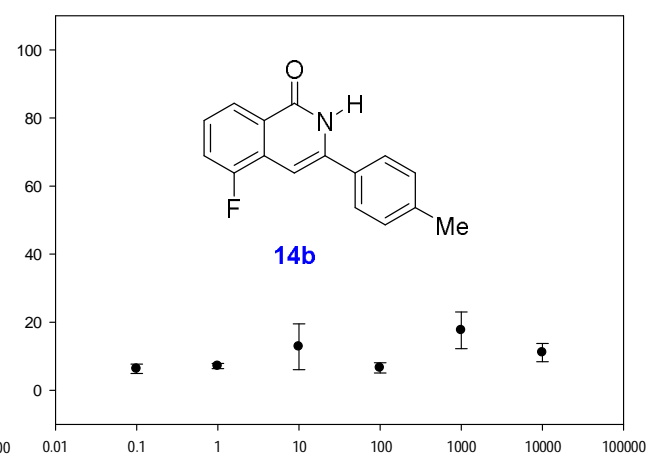
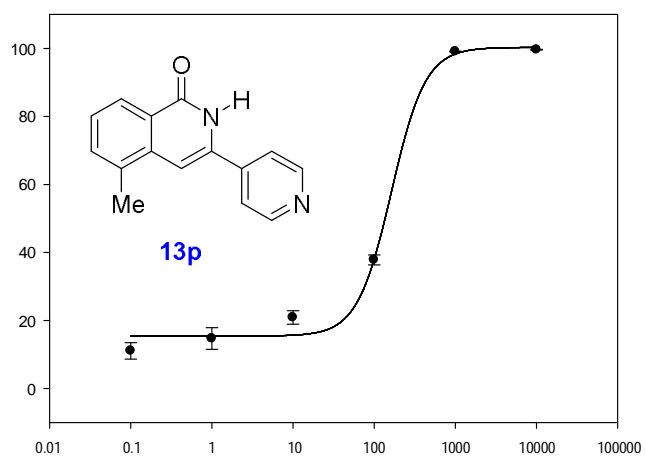
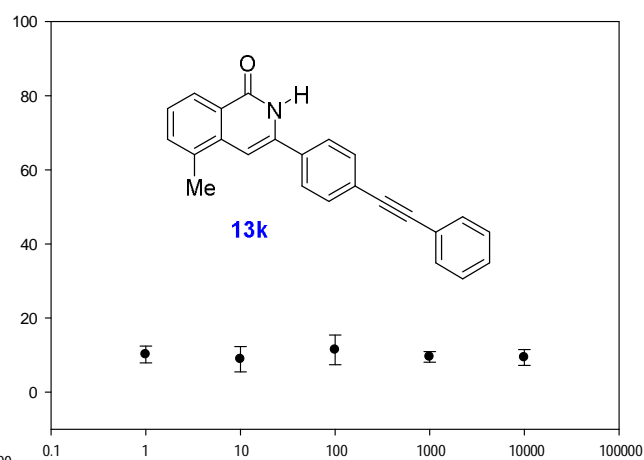
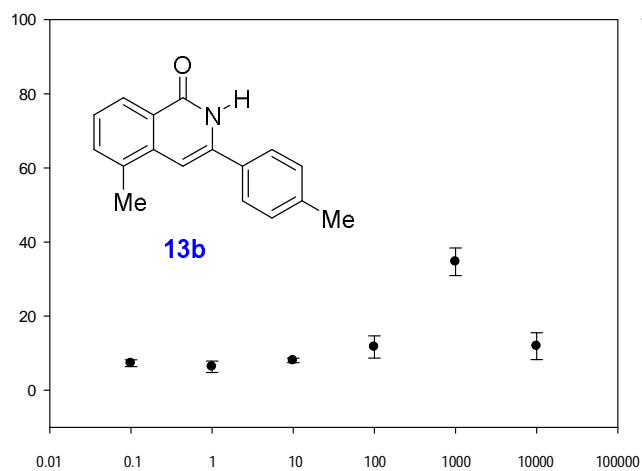


Section D: Examples of graphs of enzyme activity vs. concentration for inhibition of tankyrase-1 by isoquinolin-1-ones. X-Axes – concentration of inhibitor (nM); Y-axes – optical density (490 nm).

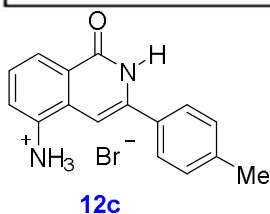
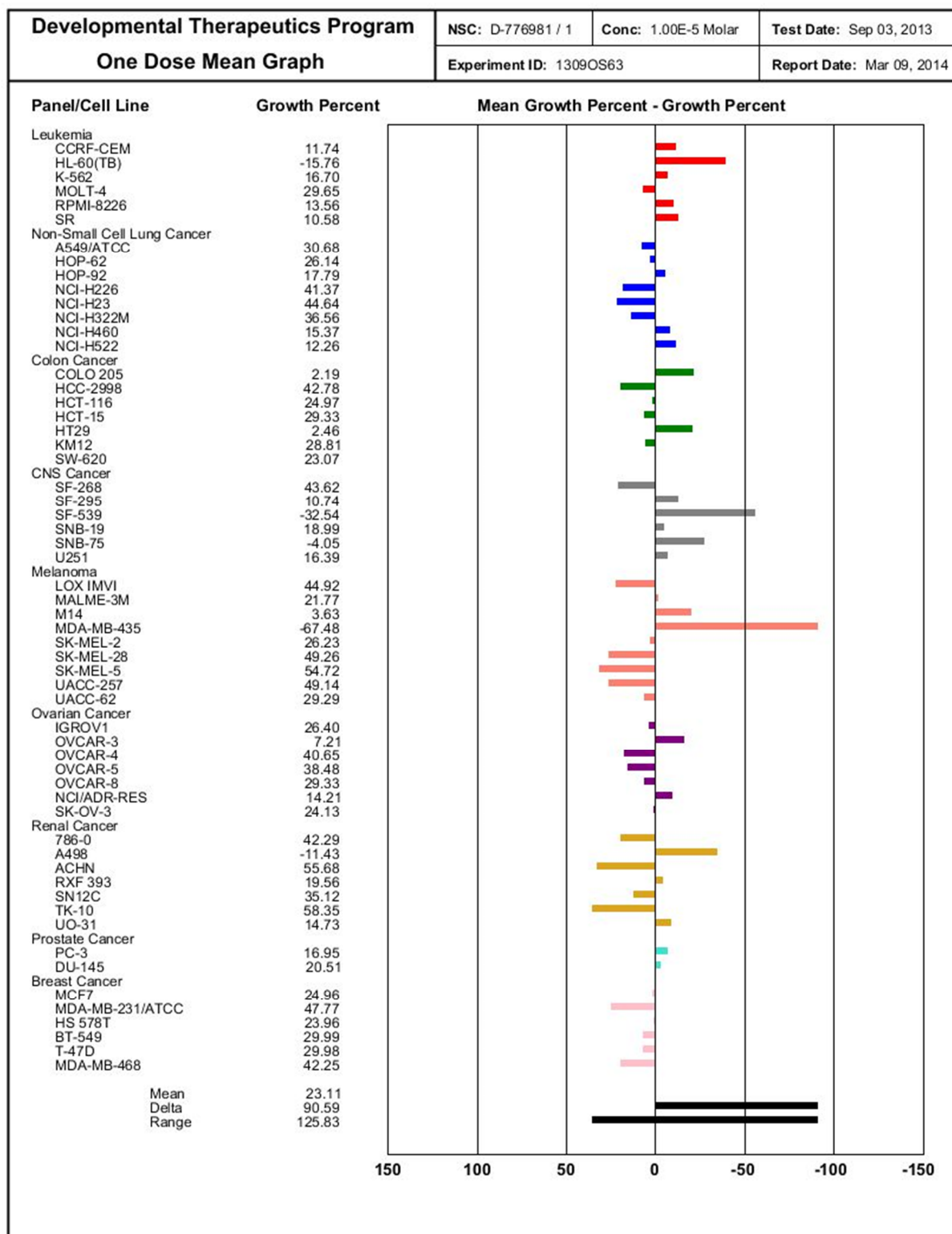




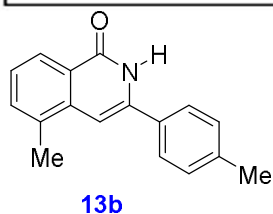
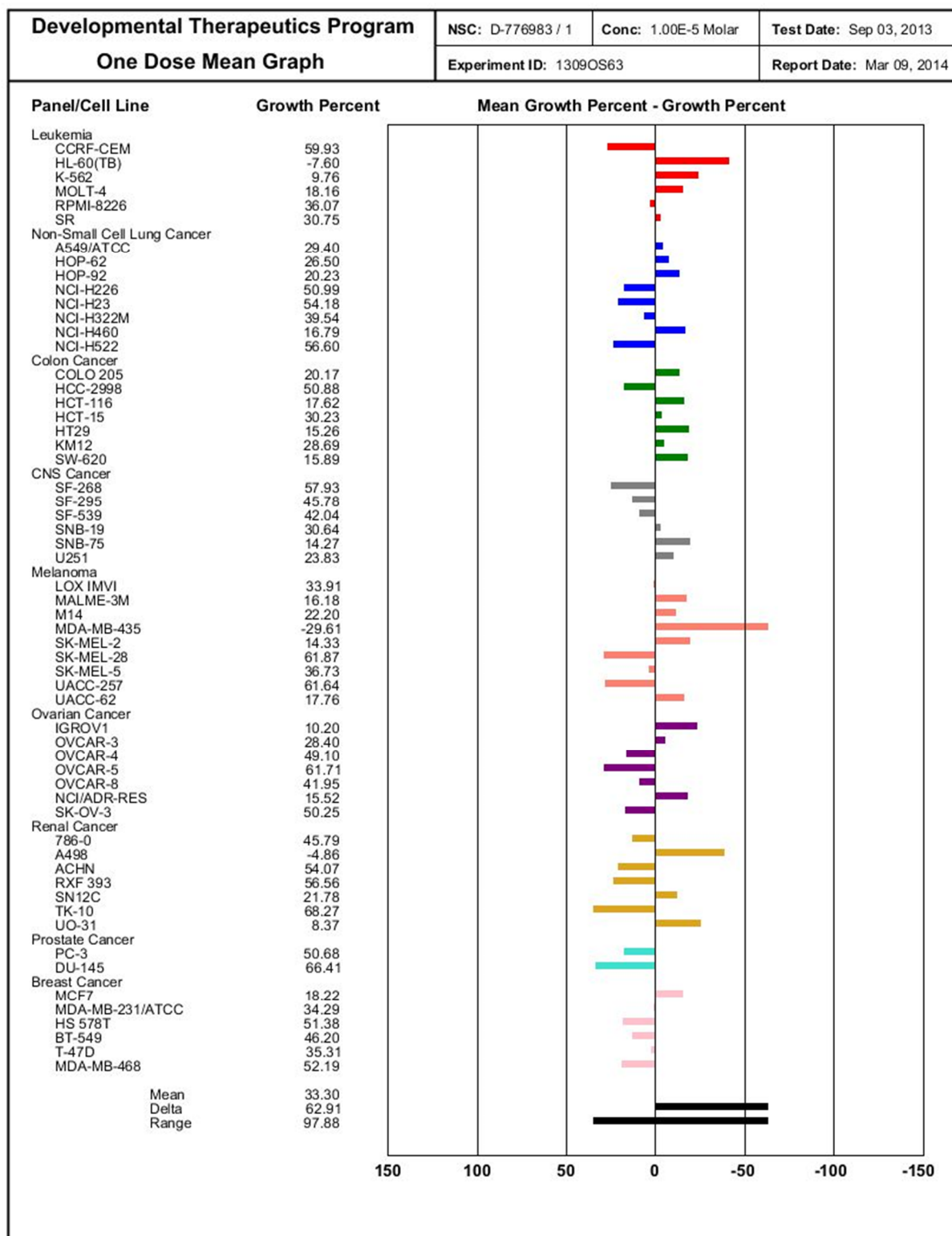
Section E: Graphs of enzyme activity vs. concentration for inhibition of human PARP-2 by isoquinolin-1-ones. X-Axes – concentration of inhibitor (nM); Y-axes – % Inhibition.



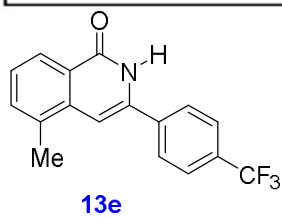
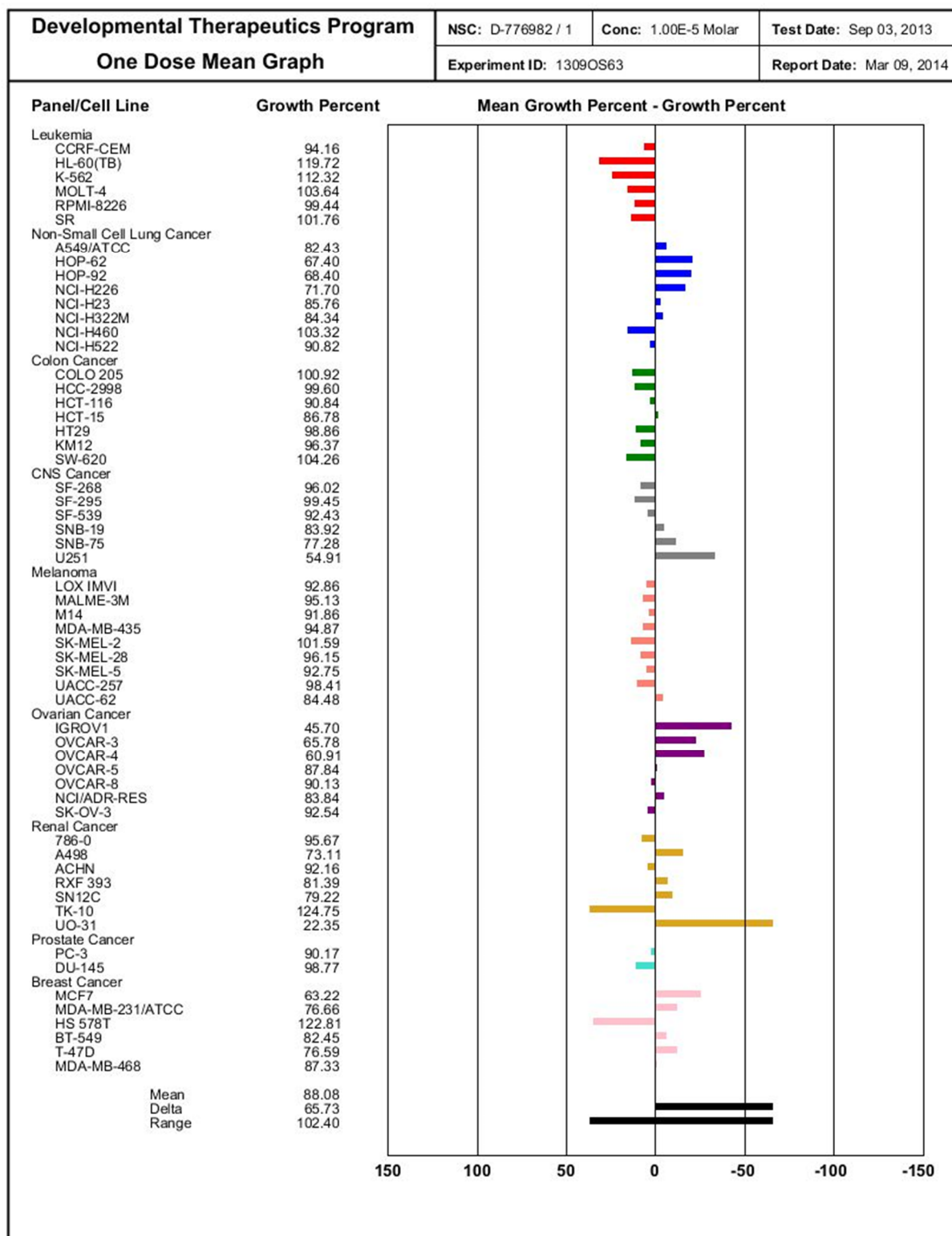
Section F: Data from NCI 60-cell-line evaluations of selected isoquinolinones



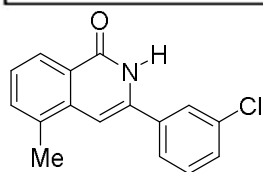
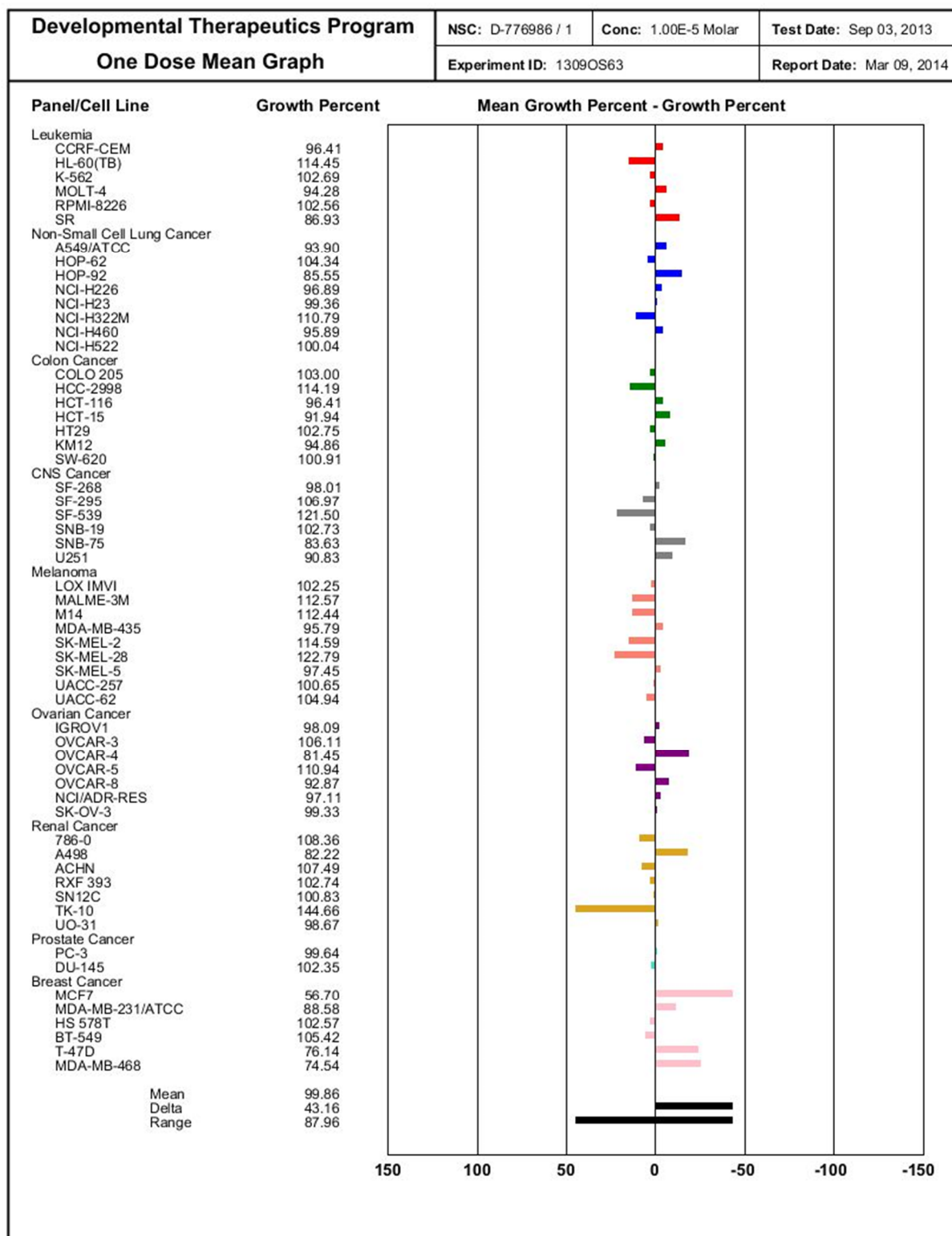
Single concentration 10 μ M



Single concentration 10 μ M

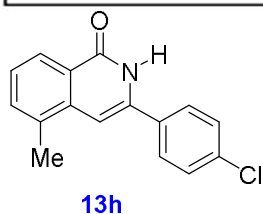
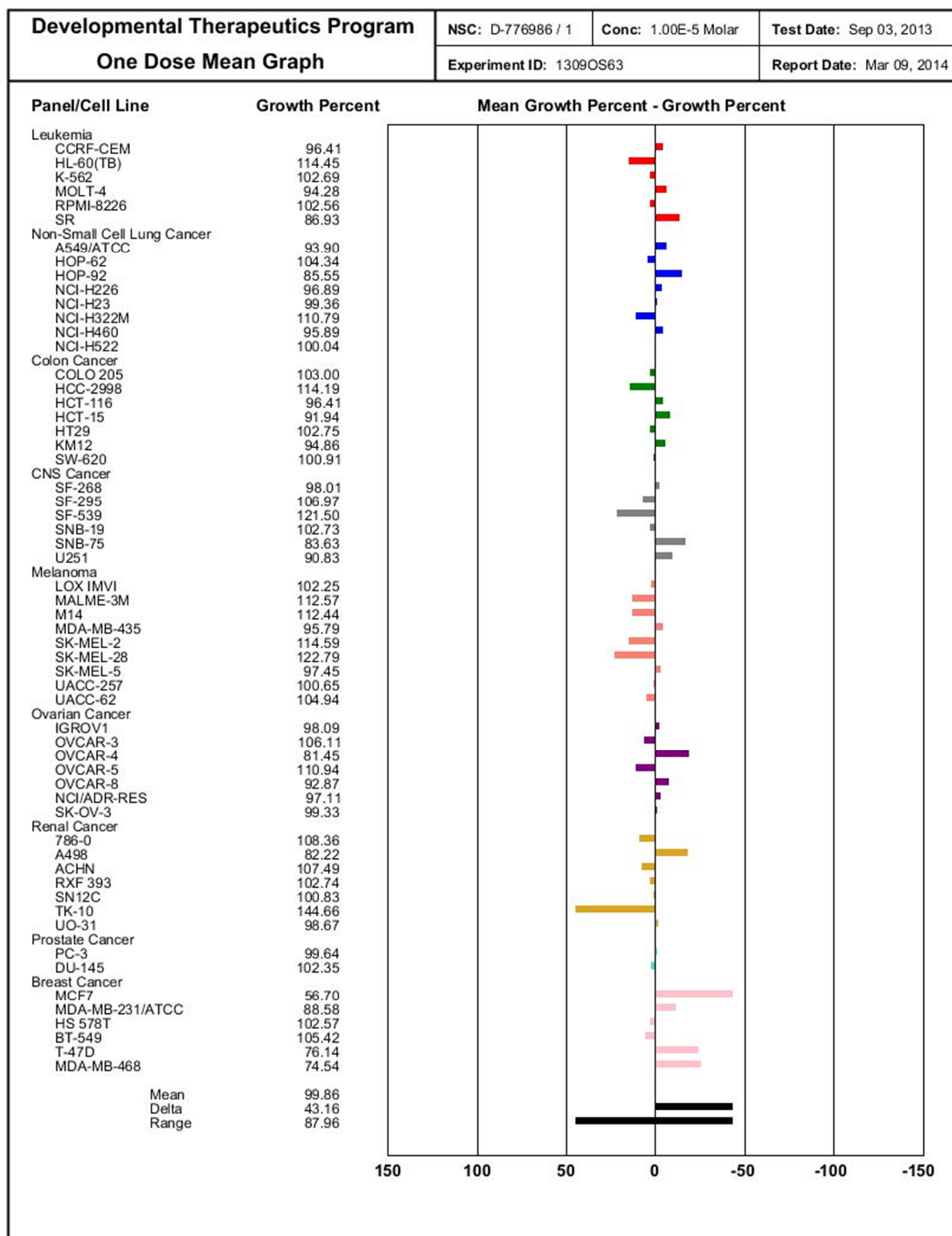


Single concentration 10 μ M

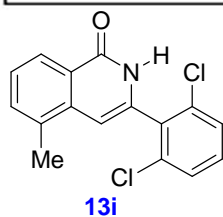
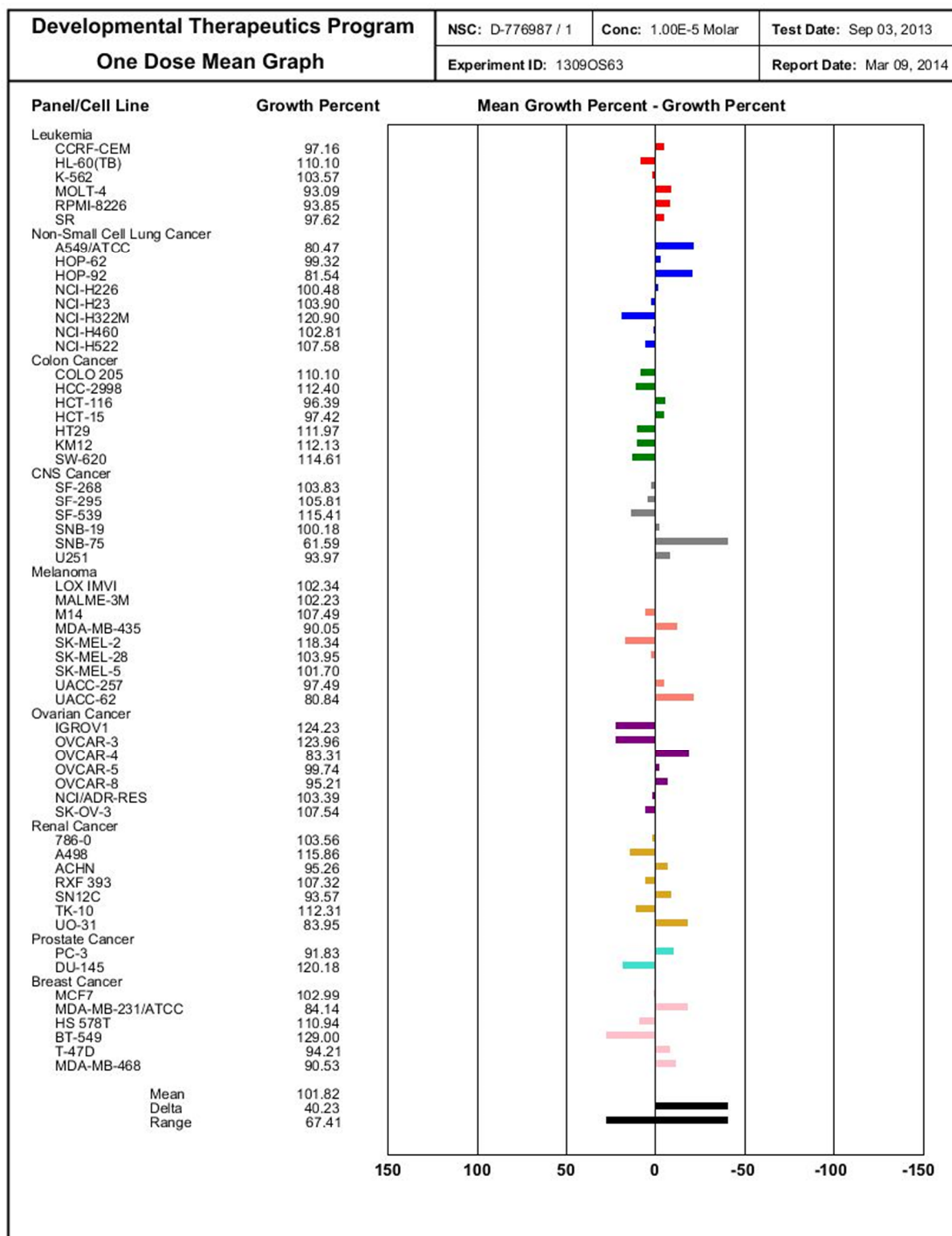


13g

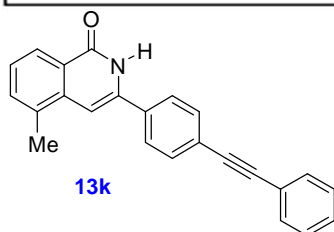
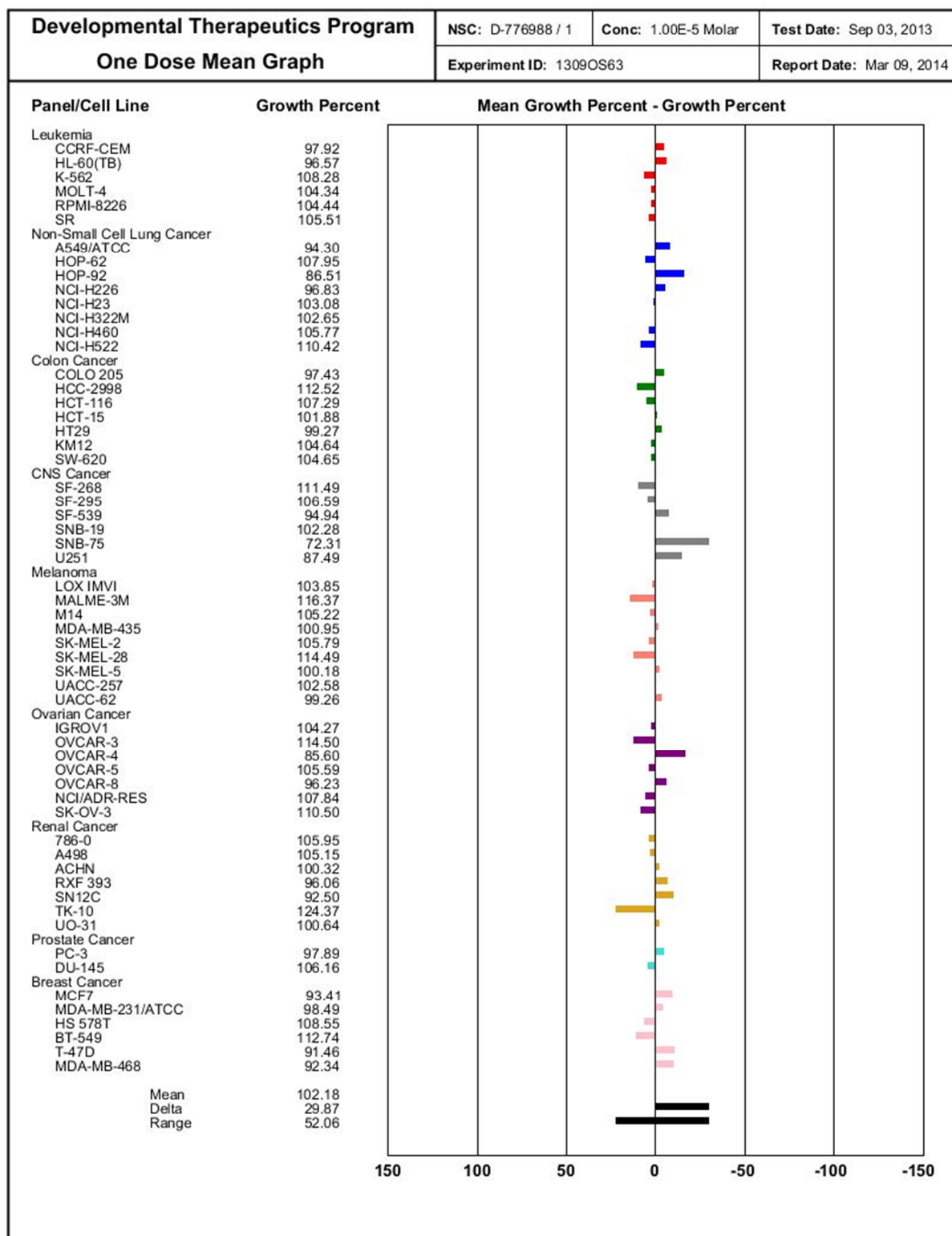
Single concentration 10 μ M



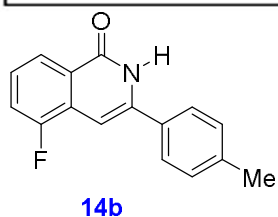
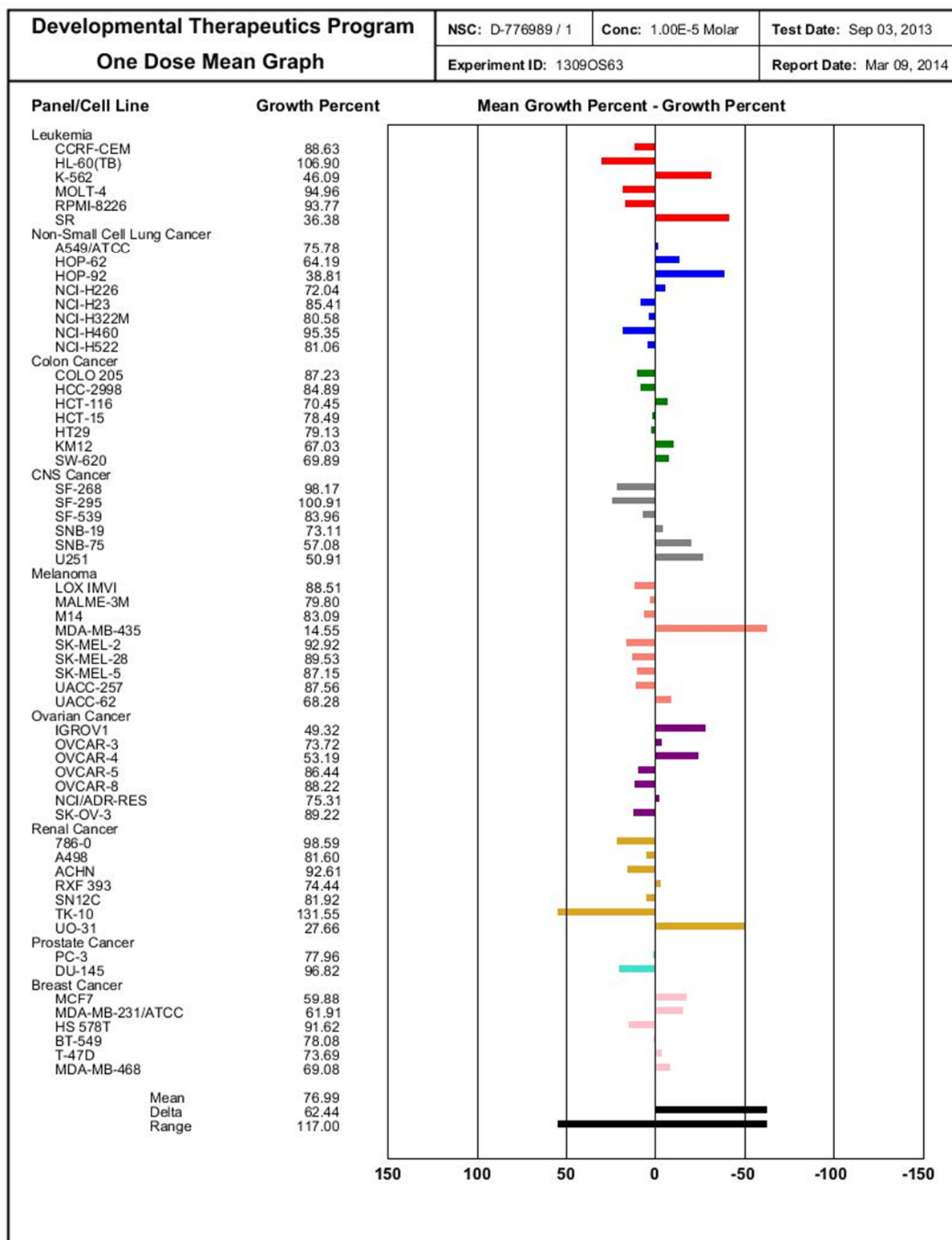
Single concentration 10 μ M



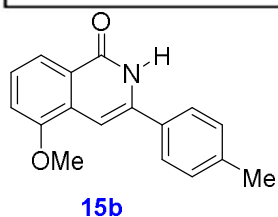
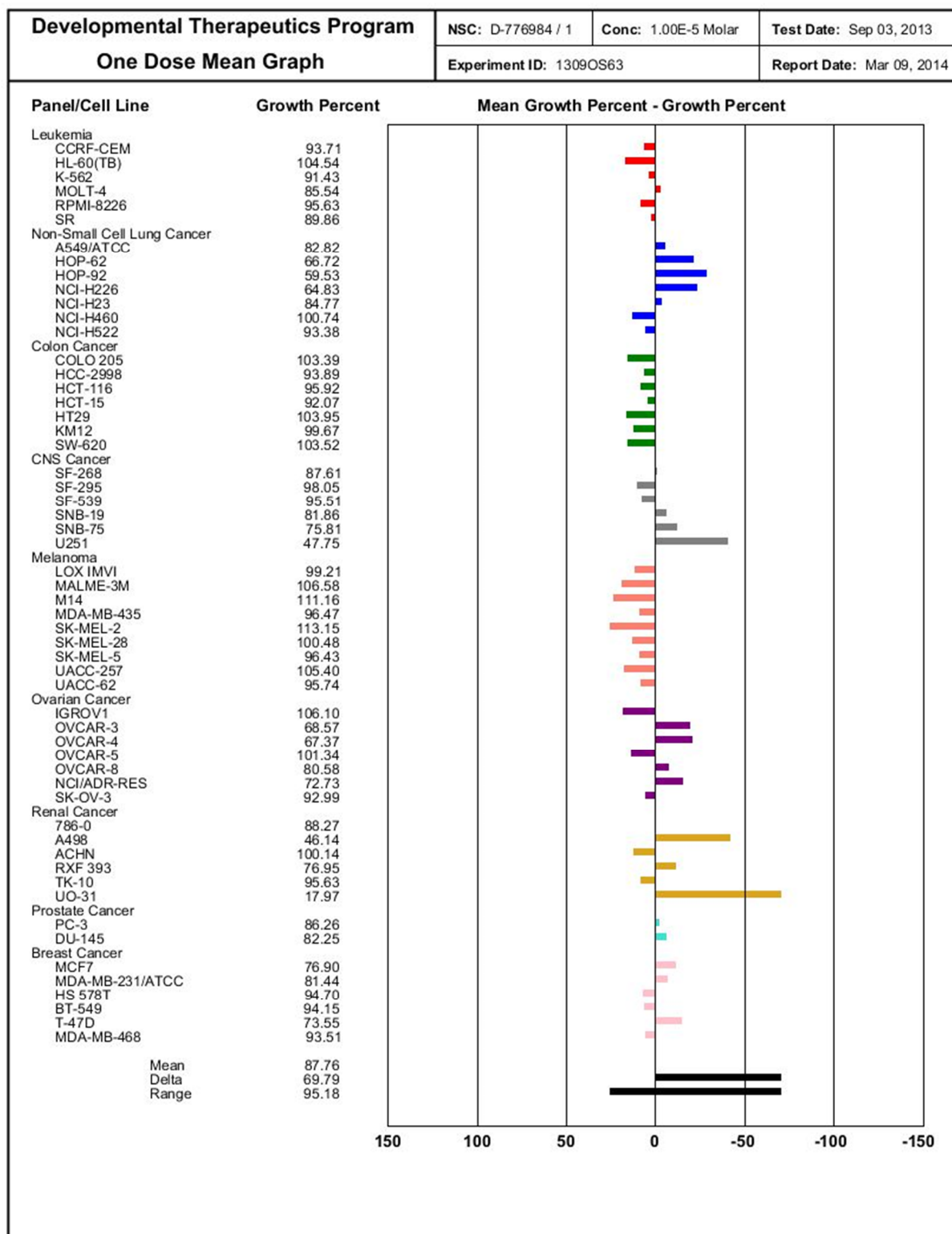
Single concentration 10 μ M



Single concentration 10 μ M

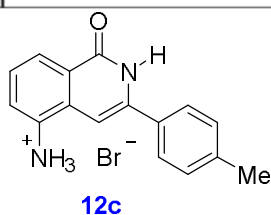


Single concentration 10 μ M



Single concentration 10 μ M

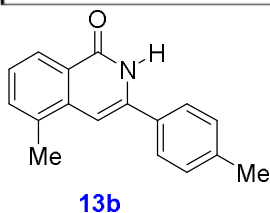
National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results																
NSC : D - 776981 / 1			Experiment ID : 1312NG05					Test Type : 08				Units : Molar				
Report Date : February 14, 2014			Test Date : December 30, 2013					QNS :				MC :				
COMI : HAP2-135 (132198)			Stain Reagent : SRB Dual-Pass Related					SSPL : OFMB								
Panel/Cell Line	Time	Zero	Ctrl	Log10 Concentration					Percent Growth					GI50	TGI	LC50
				-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0			
Leukemia																
CCRF-CEM	0.377	2.216	2.104	2.122	1.585	0.445	0.450	94	95	86	4	4	1.79E-6	> 1.00E-4	> 1.00E-4	
HL-60(TB)	1.300	3.338	3.277	3.345	2.665	1.015	1.352	97	100	66	-22	3	1.56E-6	> 1.00E-4	> 1.00E-4	
K-562	0.373	2.432	2.426	2.172	1.438	0.537	0.550	100	87	52	8	9	1.06E-6	> 1.00E-4	> 1.00E-4	
MOLT-4	0.716	2.636	2.669	2.624	2.359	0.846	0.756	102	99	86	7	2	2.83E-6	> 1.00E-4	> 1.00E-4	
RFM-8226	0.985	2.946	2.921	2.901	2.664	1.292	1.066	99	98	86	15	5	3.20E-6	> 1.00E-4	> 1.00E-4	
SR	0.498	2.418	2.273	2.201	1.129	0.485	0.415	92	89	33	-3	-17	4.93E-7	8.39E-6	> 1.00E-4	
Non-Small Cell Lung Cancer																
A549ATCC	0.440	2.251	2.221	2.221	1.993	0.709	0.589	98	98	86	15	8	3.19E-6	> 1.00E-4	> 1.00E-4	
HOP-62	0.520	1.813	1.808	1.736	1.480	0.829	0.736	100	94	74	24	17	3.03E-6	> 1.00E-4	> 1.00E-4	
HOP-62	1.452	2.004	1.935	1.936	1.796	1.523	1.547	88	88	62	13	17	1.78E-6	> 1.00E-4	> 1.00E-4	
NCI-H226	1.160	2.705	2.657	2.660	2.454	1.855	1.713	97	97	84	45	36	7.47E-6	> 1.00E-4	> 1.00E-4	
NCI-H23	0.564	1.604	1.590	1.599	1.533	0.988	0.905	99	99	93	41	33	6.65E-6	> 1.00E-4	> 1.00E-4	
NCI-H222M	0.827	1.928	1.889	1.839	1.749	1.418	1.538	94	92	84	54	65	> 1.00E-4	> 1.00E-4	> 1.00E-4	
NCI-H460	0.266	2.653	2.703	2.774	2.587	0.494	0.327	102	105	97	10	3	3.46E-6	> 1.00E-4	> 1.00E-4	
NCI-H522	0.891	2.260	2.210	2.232	1.991	1.007	0.848	96	96	80	8	-5	2.66E-6	4.31E-5	> 1.00E-4	
Colon Cancer																
COLO 205	0.459	1.607	1.695	1.582	1.456	0.408	0.309	105	95	87	-11	-33	2.38E-6	7.70E-6	> 1.00E-4	
HCC-2998	0.590	1.837	1.693	1.802	1.525	0.759	0.659	88	97	75	14	6	2.55E-6	> 1.00E-4	> 1.00E-4	
HCT-116	0.267	2.274	2.263	2.129	1.438	0.437	0.448	99	93	56	8	9	1.47E-6	> 1.00E-4	> 1.00E-4	
HCT-116	0.370	2.036	1.693	1.882	1.261	0.818	0.567	91	91	83	15	11	1.19E-6	> 1.00E-4	> 1.00E-4	
HT29	0.306	1.664	1.675	1.768	1.653	0.358	0.364	101	108	99	4	6	3.28E-6	> 1.00E-4	> 1.00E-4	
KM12	0.476	2.457	2.362	2.411	1.648	0.862	0.743	96	95	59	19	13	1.70E-6	> 1.00E-4	> 1.00E-4	
SW-620	0.255	1.888	1.898	1.815	1.248	0.596	0.617	98	96	61	21	22	1.87E-6	> 1.00E-4	> 1.00E-4	
CNS Cancer																
SF-298	0.609	2.010	1.962	1.911	1.727	1.211	0.940	97	93	80	43	24	6.44E-6	> 1.00E-4	> 1.00E-4	
SF-298	0.613	2.796	2.637	2.500	2.164	0.567	0.594	93	86	71	-6	-3	1.86E-6	8.01E-6	> 1.00E-4	
SNB-19	0.742	2.514	2.396	2.442	2.178	1.295	1.367	93	95	81	31	35	4.13E-6	> 1.00E-4	> 1.00E-4	
SNB-75	0.846	1.764	1.687	1.572	1.465	0.819	0.763	92	79	67	-3	-6	1.76E-6	8.95E-6	> 1.00E-4	
U871	0.460	2.269	2.237	2.226	1.596	0.751	0.845	97	97	62	16	21	1.83E-6	> 1.00E-4	> 1.00E-4	
Melanoma																
LOX IMVI	0.291	1.682	1.602	1.664	1.425	0.787	0.580	94	99	82	36	21	4.86E-6	> 1.00E-4	> 1.00E-4	
MALME-3M	0.814	1.392	1.345	1.342	1.274	1.138	1.241	92	91	80	56	74	> 1.00E-4	> 1.00E-4	> 1.00E-4	
M14	0.488	2.146	2.052	1.982	1.420	0.761	0.941	94	90	56	16	27	1.43E-6	> 1.00E-4	> 1.00E-4	
MDA-MB-435	0.558	2.683	2.593	2.482	0.614	0.315	0.573	96	91	3	-44	1	2.80E-7		> 1.00E-4	
SK-MEL-5	0.646	3.060	3.125	3.129	1.835	1.164	0.311	102	102	49	21	-52	9.52E-7	1.96E-5	9.41E-5	
UACC-257	0.994	2.402	2.296	2.356	2.123	1.835	1.790	92	97	80	60	57	> 1.00E-4	> 1.00E-4	> 1.00E-4	
UACC-62	1.154	2.780	2.720	2.713	2.252	1.770	1.778	96	96	68	38	38	3.90E-6	> 1.00E-4	> 1.00E-4	
Ovarian Cancer																
IGROV1	0.774	2.252	2.222	2.236	1.968	1.250	1.049	98	99	81	32	19	4.30E-6	> 1.00E-4	> 1.00E-4	
OVCA9-3	0.462	1.647	1.630	1.607	1.353	0.571	0.602	99	97	75	9	19	2.41E-6	> 1.00E-4	> 1.00E-4	
OVCA9-4	0.678	1.324	1.289	1.223	1.170	0.920	0.793	95	94	75	37	18	4.72E-6	> 1.00E-4	> 1.00E-4	
OVCA9-8	0.560	2.518	2.476	2.493	2.292	1.061	0.914	98	99	88	26	18	4.06E-6	> 1.00E-4	> 1.00E-4	
NCIADR-RES	0.847	2.346	2.263	2.297	1.870	0.963	1.017	94	97	68	8	11	2.00E-6	> 1.00E-4	> 1.00E-4	
SK-OV-3	0.967	2.295	2.183	2.036	2.001	1.261	1.253	92	80	78	22	22	3.15E-6	> 1.00E-4	> 1.00E-4	
Renal Cancer																
785-0	0.857	2.619	2.611	2.769	2.692	1.811	1.442	100	97	94	49	30	9.32E-6	> 1.00E-4	> 1.00E-4	
A498	1.760	2.429	2.248	2.252	2.075	1.554	1.531	73	74	47	-12	-13	7.71E-7	6.31E-6	> 1.00E-4	
CAK1-1	0.562	2.678	2.591	2.458	1.944	1.152	1.036	96	90	65	28	22	2.56E-6	> 1.00E-4	> 1.00E-4	
ROX-393	0.716	1.437	1.460	1.415	1.264	0.681	0.659	103	97	79	-6	20	2.21E-6	> 1.00E-4	> 1.00E-4	
SN12C	0.705	2.621	2.661	2.674	2.262	1.425	1.180	93	93	74	34	22	3.96E-6	> 1.00E-4	> 1.00E-4	
TK-10	0.862	1.833	1.847	1.921	1.923	1.297	1.066	101	109	110	43	21	7.86E-6	> 1.00E-4	> 1.00E-4	
UO-31	0.759	2.020	1.847	1.790	1.494	0.967	0.886	86	82	56	16	10	1.56E-6	> 1.00E-4	> 1.00E-4	
Prostate Cancer																
PC-3	0.648	2.476	2.389	2.353	1.857	1.067	1.093	95	93	66	23	24	2.36E-6	> 1.00E-4	> 1.00E-4	
DU-145	0.290	1.340	1.336	1.355	1.260	0.568	0.516	100	101	92	26	21	4.40E-6	> 1.00E-4	> 1.00E-4	
Breast Cancer																
MC77	0.321	1.749	1.600	1.550	1.218	0.512	0.479	90	85	63	13	11	1.81E-6	> 1.00E-4	> 1.00E-4	
MDA-MB-231/ATCC	0.735	1.844	1.837	1.726	1.413	0.850	0.902	99	89	61	19	15	1.86E-6	> 1.00E-4	> 1.00E-4	
HS 578T	1.382	2.490	2.434	2.402	2.217	1.532	1.527	95	92	75	14	13	2.57E-6	> 1.00E-4	> 1.00E-4	
BT-549	1.098	2.011	2.009	1.891	1.669	1.145	1.101	100	87	63	5	-	1.66E-6	> 1.00E-4	> 1.00E-4	
T-47D	0.813	1.822	1.746	1.654	1.649	1.220	1.156	92	83	83	40	34	5.91E-6	> 1.00E-4	> 1.00E-4	
MDA-MB-468	0.800	1.509	1.480	1.470	1.399	0.853	0.895	96	94	84	9	13	2.66E-6	> 1.00E-4	> 1.00E-4	



Five concentrations:

10 nM, 100 nM, 1.0 μ M, 10 μ M, 100 μ M

National Cancer Institute Developmental Therapeutics Program In-Vitro Testing Results																
NSC : D - 776983 / 1			Experiment ID : 140INS08						Test Type : 08				Units : Molar			
Report Date : February 14, 2014			Test Date : January 06, 2014						QNS :				MC :			
COMI : HAP4-093 (132200)			Stain Reagent : SRB Dual-Pass Related						SSPL : OFMB							
Log10 Concentration																
Panel/Cell Line	Time	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-3.0	-2.0	-1.0	-0.0	-1.0	-2.0	GI50	TDI	LC50
Leukemia																
CCRF-CEM	0.703	3.042	3.040	3.040	2.953	1.520	1.260	100	100	97	35	24	5.69E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
K-562	0.162	1.747	1.909	1.823	0.895	0.458	0.356	110	105	46	19	12	8.62E-7	> 1.00E-4	> 1.00E-4	> 1.00E-4
MOLT-4	0.554	2.595	2.700	2.650	2.607	1.150	1.066	105	103	101	29	25	5.11E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
RFPM-8226	1.056	2.893	2.826	2.888	2.746	1.548	1.344	96	100	92	27	16	4.40E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SR	0.412	1.396	1.436	1.439	1.069	0.440	0.379	104	104	89	3	-8	1.92E-6	1.81E-5	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer																
A549ATCC	0.432	2.110	2.094	2.111	1.793	0.999	0.966	99	100	81	34	32	4.54E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
HOP-62	0.733	1.490	1.340	1.289	1.129	0.936	0.926	80	73	52	27	26	1.23E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
HOP-62	1.618	2.015	1.970	1.854	1.749	1.489	1.535	89	82	33	-8	-5	2.58E-7	6.39E-6	> 1.00E-4	> 1.00E-4
NCH-H226	1.070	2.779	2.704	2.506	2.353	1.805	1.874	96	84	75	43	47	6.04E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCH-H23	0.510	1.509	1.532	1.508	1.411	0.939	0.886	102	100	90	43	38	7.06E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCH-H222M	1.060	2.250	2.230	2.180	1.952	1.721	1.686	98	94	77	56	53	> 1.00E-4	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCH-H460	0.336	2.866	2.970	2.896	2.667	0.742	0.741	104	101	93	16	16	3.62E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCH-H522	0.934	2.467	2.408	2.350	2.203	0.825	0.796	96	92	83	-12	-15	2.22E-6	7.51E-6	> 1.00E-4	> 1.00E-4
Colon Cancer																
COLO 205	0.405	1.465	1.336	1.363	1.251	0.507	0.464	88	90	80	10	7	2.66E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
HCC-2998	0.432	1.262	1.296	1.278	1.252	0.928	1.047	102	100	97	58	72	> 1.00E-4	> 1.00E-4	> 1.00E-4	> 1.00E-4
HCT-116	0.300	2.468	2.336	2.342	1.973	0.800	0.780	93	93	76	23	21	3.12E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
HCT-15	0.322	1.919	1.804	1.736	1.468	0.586	0.622	93	88	72	17	19	2.47E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
HT29	0.247	1.329	1.414	1.307	1.248	0.418	0.339	108	98	92	16	9	3.58E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
KM12	0.610	2.780	2.777	2.809	2.185	1.317	1.163	100	101	72	33	25	3.58E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SW-620	0.380	2.193	2.163	2.110	1.578	0.686	0.602	98	95	86	17	12	2.12E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
CNS Cancer																
SF-298	0.589	1.857	1.806	1.776	1.694	1.077	1.037	96	94	87	38	35	5.80E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SF-296	0.517	2.498	2.260	2.277	2.059	0.790	0.740	88	89	78	14	11	2.75E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SF-639	1.021	2.713	2.550	2.586	2.486	1.000	0.974	90	92	87	-2	-5	2.56E-6	9.48E-6	> 1.00E-4	> 1.00E-4
SNB-19	0.787	2.462	2.419	2.220	1.869	1.366	1.454	97	86	65	35	40	3.07E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SNB-75	0.649	1.368	1.248	1.258	1.155	0.500	0.519	80	81	68	-23	-20	1.56E-6	5.57E-6	> 1.00E-4	> 1.00E-4
U871	0.964	2.326	2.278	1.790	1.464	1.004	1.043	97	70	51	25	27	1.10E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
Melanoma																
LOX IMVI	0.231	1.442	1.476	1.420	1.323	0.684	0.679	103	98	90	37	37	5.77E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
MALME-3M	0.695	1.212	1.252	1.215	1.177	0.939	0.889	108	101	93	48	35	9.08E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
M14	0.584	2.260	2.115	2.125	1.793	0.775	0.794	91	92	72	11	13	2.32E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
MDA-MB-435	0.538	2.411	2.296	2.256	0.892	0.297	0.295	94	92	8	-45	-45	3.16E-7	1.43E-6	> 1.00E-4	> 1.00E-4
SK-MEL-2	1.009	1.896	1.996	1.947	1.852	1.120	1.051	111	106	96	13	5	3.56E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-MEL-28	0.537	1.610	1.586	1.583	1.410	0.968	1.015	95	97	81	40	45	5.78E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-MEL-5	0.681	2.460	2.393	2.284	1.911	0.962	0.962	96	90	69	17	17	2.32E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
UACC-257	0.944	1.952	1.952	1.924	1.766	1.393	1.443	100	94	79	43	48	6.46E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
UACC-62	0.904	2.587	2.435	2.278	2.023	1.504	1.557	91	82	67	36	39	3.43E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
Ovarian Cancer																
IGROV1	0.882	2.466	2.487	2.391	2.011	1.418	1.379	101	95	71	34	31	3.70E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
OVCA1-3	0.579	1.730	1.757	1.566	1.385	0.549	0.462	102	86	70	-8	-17	1.94E-6	8.51E-6	> 1.00E-4	> 1.00E-4
OVCA1-4	0.641	1.431	1.344	1.302	1.101	0.949	0.976	89	84	58	39	42	2.68E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
OVCA1-5	0.785	1.718	1.623	1.658	1.505	1.193	1.254	90	94	78	45	51	> 1.00E-4	> 1.00E-4	> 1.00E-4	> 1.00E-4
OVCA1-6	0.643	2.494	2.466	2.252	2.145	1.154	1.230	98	87	81	28	32	3.82E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCIADR-RES	0.567	1.760	1.762	1.606	1.472	0.672	0.689	100	87	76	9	10	2.43E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-OV-3	0.918	2.147	2.028	1.996	1.738	1.145	1.220	90	88	67	19	25	2.23E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
Renal Cancer																
785-O	0.719	2.668	2.664	2.644	2.440	1.466	1.526	100	99	86	38	41	5.84E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
A498	1.640	2.239	2.214	2.178	2.022	1.389	1.425	96	90	83	-16	-14	1.47E-6	6.31E-6	> 1.00E-4	> 1.00E-4
ACHN	0.425	2.005	1.900	1.950	1.876	1.049	1.046	93	97	92	39	39	6.25E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
CAPO-1	0.684	2.825	2.554	2.406	2.129	1.026	1.061	87	80	67	16	18	2.18E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
ROX 393	0.911	1.877	1.842	1.697	1.592	1.147	1.105	96	81	70	24	20	2.78E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
SN12C	0.794	2.676	2.494	2.261	2.094	1.377	1.465	90	78	69	31	36	3.16E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
TK-10	0.637	1.442	1.474	1.503	1.373	0.895	0.874	104	108	91	31	29	4.82E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
UO-31	0.907	2.242	2.003	1.795	1.390	1.097	0.966	82	66	36	14	6	3.41E-7	> 1.00E-4	> 1.00E-4	> 1.00E-4
Prostate Cancer																
PC-3	0.770	2.695	2.515	2.442	2.265	1.320	1.335	91	87	78	29	29	3.66E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
DU-145	0.365	1.440	1.496	1.406	1.292	0.662	0.584	105	97	86	28	20	4.15E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
Breast Cancer																
MCF7	0.469	2.510	2.236	2.331	1.993	0.739	0.789	87	91	75	13	16	2.52E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
MDA-MB-231ATCC	0.764	1.965	2.013	1.726	1.414	1.250	1.247	102	79	53	40	40	1.75E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
HS 578T	1.545	2.453	2.288	2.283	2.271	1.626	1.544	82	81	80	9	.	2.64E-6	9.99E-6	> 1.00E-4	> 1.00E-4
BT-549	0.595	1.451	1.361	1.338	1.227	0.776	0.745	89	87	74	21	17	2.84E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
T-47D	0.529	1.116	1.036	1.075	0.969	0.725	0.745	86	93	75	33	37	3.96E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4
MDA-MB-468	0.645	1.331	1.268	1.252	1.178	0.803	0.758	91	88	78	23	16	3.18E-6	> 1.00E-4	> 1.00E-4	> 1.00E-4



Section G: Crystal data for small-molecule X-ray crystallography

Table 1. Crystal data and structure refinement for **13i**.

Identification code	k12farm8
Empirical formula	C ₃₄ H ₂₈ Cl ₄ N ₂ O ₃
Formula weight	654.38
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2 ₁ /n
Unit cell dimensions	a = 14.1190(3) Å α = 90° b = 13.6440(3) Å β = 96.302(1)° c = 15.7740(4) Å γ = 90°
Volume	3020.33(12) Å ³
Z	4
Density (calculated)	1.439 Mg m ⁻³
Absorption coefficient	0.431 mm ⁻¹
F(000)	1352
Crystal size	0.25 × 0.15 × 0.08 mm
θ range for data collection	3.62 to 26.37°
Index ranges	-17 ≤ h ≤ 17; -17 ≤ k ≤ 17; -19 ≤ l ≤ 19
Reflections collected	56157
Independent reflections	6157 [R(int) = 0.0932]
Reflections observed (>2 σ)	4274
Data Completeness	0.997
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928 and 0.832
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6157 / 0 / 391
Goodness-of-fit on F ²	1.034
Final R indices [I>2 σ (I)]	R1 = 0.0502 wR2 = 0.1070
R indices (all data)	R1 = 0.0868 wR2 = 0.1250
Largest diff. peak and hole	0.382 and -0.377 eÅ ⁻³

Notes:

Small crystal – poor diffraction at higher Bragg angles, hence data truncated at $\theta = 26.4^\circ$. Two molecules in the asymmetric unit plus one solvent entity (ethanol). Hydrogen-bonding present. Methyl hydrogen atoms attached to C16 and C16A are disordered.

D-H	d(D-H)	d(H...A)	<DHA	d(D...A)	A
O2-H2	0.840	1.988	174.03	2.825	O1A
N1-H1	0.880	1.947	170.53	2.819	O1A
N1A-H1A	0.880	2.030	160.14	2.874	O1

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 1.U(eq) is defined as one third of the trace of the orthogonallised Uij tensor for **13i**.

Atom	x	y	z	U(eq)
Cl(1)	6739(1)	6508(1)	5251(1)	43(1)
Cl(2)	6779(1)	3145(1)	7104(1)	35(1)
O(1)	8901(1)	2703(1)	5088(1)	30(1)
O(2)	6729(2)	3007(2)	3249(2)	51(1)
N(1)	7908(2)	3810(2)	5586(1)	26(1)
C(1)	6168(2)	5613(2)	5800(2)	31(1)
C(2)	5211(2)	5739(2)	5874(2)	34(1)
C(3)	4733(2)	5046(2)	6300(2)	38(1)
C(4)	5216(2)	4233(2)	6660(2)	36(1)
C(5)	6181(2)	4132(2)	6585(2)	29(1)
C(6)	6690(2)	4804(2)	6142(2)	26(1)
C(7)	7708(2)	4650(2)	6035(2)	25(1)
C(8)	8425(2)	5243(2)	6344(2)	26(1)
C(9)	9396(2)	5012(2)	6224(2)	24(1)
C(10)	9587(2)	4125(2)	5812(2)	25(1)
C(11)	8802(2)	3491(2)	5473(2)	26(1)
C(12)	10522(2)	3860(2)	5709(2)	30(1)
C(13)	11260(2)	4467(2)	6004(2)	33(1)
C(14)	11076(2)	5357(2)	6393(2)	32(1)
C(15)	10161(2)	5644(2)	6503(2)	26(1)
C(16)	9966(2)	6627(2)	6895(2)	34(1)
C(17)	7352(2)	2287(2)	2980(2)	47(1)
C(18)	7566(3)	2559(3)	2092(2)	51(1)
Cl(1A)	8342(1)	-1484(1)	5145(1)	38(1)
Cl(2A)	8970(1)	1794(1)	7072(1)	38(1)
O(1A)	6463(1)	2497(1)	4942(1)	29(1)
N(1A)	7483(2)	1314(2)	5481(1)	25(1)
C(1A)	9101(2)	-663(2)	5728(2)	26(1)
C(2A)	10060(2)	-884(2)	5836(2)	30(1)
C(3A)	10687(2)	-241(2)	6291(2)	34(1)
C(4A)	10352(2)	597(2)	6654(2)	33(1)
C(5A)	9385(2)	789(2)	6545(2)	28(1)
C(6A)	8723(2)	187(2)	6066(2)	25(1)
C(7A)	7699(2)	449(2)	5932(2)	25(1)
C(8A)	6993(2)	-75(2)	6225(2)	25(1)
C(9A)	6024(2)	259(2)	6099(2)	24(1)

C(10A)	5826(2)	1162(2)	5674(2)	24(1)
C(11A)	6594(2)	1704(2)	5340(2)	25(1)
C(12A)	4902(2)	1535(2)	5562(2)	29(1)
C(13A)	4173(2)	1015(2)	5849(2)	31(1)
C(14A)	4353(2)	114(2)	6253(2)	32(1)
C(15A)	5261(2)	-279(2)	6385(2)	27(1)
C(16A)	5426(2)	-1265(2)	6805(2)	35(1)

Table 3. Bond lengths [Å] and angles [°] for **13i**.

Cl(1)-C(1)	1.745(3)	Cl(2)-C(5)	1.744(3)
O(1)-C(11)	1.250(3)	O(2)-C(17)	1.414(4)
N(1)-C(11)	1.366(3)	N(1)-C(7)	1.392(3)
C(1)-C(2)	1.380(4)	C(1)-C(6)	1.402(4)
C(2)-C(3)	1.378(4)	C(3)-C(4)	1.391(4)
C(4)-C(5)	1.388(4)	C(5)-C(6)	1.398(4)
C(6)-C(7)	1.481(4)	C(7)-C(8)	1.345(4)
C(8)-C(9)	1.439(4)	C(9)-C(10)	1.414(4)
C(9)-C(15)	1.414(4)	C(10)-C(12)	1.396(4)
C(10)-C(11)	1.461(4)	C(12)-C(13)	1.371(4)
C(13)-C(14)	1.398(4)	C(14)-C(15)	1.379(4)
C(15)-C(16)	1.514(4)	C(17)-C(18)	1.511(5)
Cl(1A)-C(1A)	1.741(3)	Cl(2A)-C(5A)	1.737(3)
O(1A)-C(11A)	1.254(3)	N(1A)-C(11A)	1.360(3)
N(1A)-C(7A)	1.394(3)	C(1A)-C(2A)	1.381(4)
C(1A)-C(6A)	1.405(4)	C(2A)-C(3A)	1.388(4)
C(3A)-C(4A)	1.384(4)	C(4A)-C(5A)	1.384(4)
C(5A)-C(6A)	1.401(4)	C(6A)-C(7A)	1.482(4)
C(7A)-C(8A)	1.349(4)	C(8A)-C(9A)	1.435(4)
C(9A)-C(15A)	1.417(4)	C(9A)-C(10A)	1.416(4)
C(10A)-C(12A)	1.394(4)	C(10A)-C(11A)	1.457(4)
C(12A)-C(13A)	1.367(4)	C(13A)-C(14A)	1.394(4)
C(14A)-C(15A)	1.385(4)	C(15A)-C(16A)	1.506(4)
C(11)-N(1)-C(7)	124.8(2)	C(2)-C(1)-C(6)	122.9(3)
C(2)-C(1)-Cl(1)	117.7(2)	C(6)-C(1)-Cl(1)	119.4(2)
C(3)-C(2)-C(1)	119.5(3)	C(2)-C(3)-C(4)	120.1(3)
C(5)-C(4)-C(3)	119.1(3)	C(4)-C(5)-C(6)	122.7(3)
C(4)-C(5)-Cl(2)	117.7(2)	C(6)-C(5)-Cl(2)	119.5(2)
C(5)-C(6)-C(1)	115.6(3)	C(5)-C(6)-C(7)	121.5(2)
C(1)-C(6)-C(7)	122.9(2)	C(8)-C(7)-N(1)	119.6(2)
C(8)-C(7)-C(6)	125.0(2)	N(1)-C(7)-C(6)	115.3(2)
C(7)-C(8)-C(9)	120.6(2)	C(10)-C(9)-C(15)	119.1(2)
C(10)-C(9)-C(8)	118.8(2)	C(15)-C(9)-C(8)	122.1(2)
C(12)-C(10)-C(9)	120.5(3)	C(12)-C(10)-C(11)	119.6(2)
C(9)-C(10)-C(11)	119.9(2)	O(1)-C(11)-N(1)	119.5(2)
O(1)-C(11)-C(10)	124.5(2)	N(1)-C(11)-C(10)	116.0(2)
C(13)-C(12)-C(10)	119.8(3)	C(12)-C(13)-C(14)	120.2(3)
C(15)-C(14)-C(13)	121.6(3)	C(14)-C(15)-C(9)	118.8(2)

C(14)-C(15)-C(16)	121.2(3)	C(9)-C(15)-C(16)	120.0(2)
O(2)-C(17)-C(18)	107.6(3)	C(11A)-N(1A)-C(7A)	124.1(2)
C(2A)-C(1A)-C(6A)	122.8(3)	C(2A)-C(1A)-Cl(1A)	117.6(2)
C(6A)-C(1A)-Cl(1A)	119.6(2)	C(1A)-C(2A)-C(3A)	119.1(3)
C(4A)-C(3A)-C(2A)	120.6(3)	C(3A)-C(4A)-C(5A)	118.8(3)
C(4A)-C(5A)-C(6A)	123.1(3)	C(4A)-C(5A)-Cl(2A)	118.0(2)
C(6A)-C(5A)-Cl(2A)	118.8(2)	C(5A)-C(6A)-C(1A)	115.5(2)
C(5A)-C(6A)-C(7A)	121.2(2)	C(1A)-C(6A)-C(7A)	123.4(2)
C(8A)-C(7A)-N(1A)	119.7(2)	C(8A)-C(7A)-C(6A)	124.7(2)
N(1A)-C(7A)-C(6A)	115.6(2)	C(7A)-C(8A)-C(9A)	121.0(2)
C(15A)-C(9A)-C(10A)	119.0(2)	C(15A)-C(9A)-C(8A)	122.6(2)
C(10A)-C(9A)-C(8A)	118.5(2)	C(12A)-C(10A)-C(9A)	120.7(3)
C(12A)-C(10A)-C(11A)	119.4(2)	C(9A)-C(10A)-C(11A)	119.8(2)
O(1A)-C(11A)-N(1A)	120.2(2)	O(1A)-C(11A)-C(10A)	123.0(2)
N(1A)-C(11A)-C(10A)	116.9(2)	C(13A)-C(12A)-C(10A)	119.7(3)
C(12A)-C(13A)-C(14A)	120.2(3)	C(15A)-C(14A)-C(13A)	122.0(3)
C(14A)-C(15A)-C(9A)	118.4(3)	C(14A)-C(15A)-C(16A)	120.6(3)
C(9A)-C(15A)-C(16A)	121.1(3)		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **13i**. The anisotropic displacement factor exponent takes the form: $-2 \text{ gpi}^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

Atom	U11	U22	U33	U23	U13	U12
Cl(1)	36(1)	30(1)	64(1)	15(1)	9(1)	7(1)
Cl(2)	43(1)	27(1)	34(1)	4(1)	7(1)	-2(1)
O(1)	36(1)	20(1)	34(1)	-4(1)	9(1)	2(1)
O(2)	54(2)	55(2)	44(2)	11(1)	14(1)	15(1)
N(1)	28(1)	19(1)	32(1)	-1(1)	4(1)	1(1)
C(1)	34(2)	25(2)	33(2)	-2(1)	4(1)	0(1)
C(2)	30(2)	35(2)	39(2)	-5(1)	4(1)	6(1)
C(3)	28(2)	47(2)	40(2)	-9(2)	7(1)	2(1)
C(4)	36(2)	39(2)	36(2)	-6(1)	9(1)	-9(1)
C(5)	33(2)	24(1)	30(2)	-6(1)	3(1)	-1(1)
C(6)	28(2)	20(1)	29(1)	-5(1)	6(1)	0(1)
C(7)	30(2)	19(1)	26(1)	2(1)	6(1)	3(1)
C(8)	31(2)	20(1)	28(1)	0(1)	4(1)	3(1)
C(9)	28(1)	22(1)	23(1)	4(1)	4(1)	2(1)
C(10)	31(2)	21(1)	24(1)	4(1)	4(1)	1(1)
C(11)	31(2)	20(1)	26(1)	5(1)	5(1)	5(1)
C(12)	33(2)	28(2)	30(2)	2(1)	8(1)	7(1)
C(13)	27(2)	37(2)	35(2)	3(1)	7(1)	5(1)
C(14)	33(2)	33(2)	29(2)	2(1)	1(1)	-2(1)
C(15)	30(2)	25(1)	24(1)	3(1)	1(1)	2(1)
C(16)	32(2)	27(2)	41(2)	-3(1)	0(1)	-3(1)
C(17)	40(2)	40(2)	61(2)	4(2)	10(2)	-1(2)
C(18)	50(2)	61(2)	44(2)	-9(2)	10(2)	-11(2)
Cl(1A)	35(1)	27(1)	53(1)	-13(1)	1(1)	1(1)
Cl(2A)	50(1)	25(1)	35(1)	-7(1)	-3(1)	5(1)
O(1A)	34(1)	20(1)	32(1)	6(1)	2(1)	4(1)
N(1A)	28(1)	19(1)	28(1)	2(1)	4(1)	3(1)
C(1A)	30(2)	20(1)	29(2)	1(1)	2(1)	0(1)
C(2A)	35(2)	22(1)	34(2)	2(1)	7(1)	7(1)
C(3A)	30(2)	35(2)	37(2)	8(1)	2(1)	3(1)
C(4A)	35(2)	30(2)	33(2)	1(1)	-2(1)	-5(1)
C(5A)	34(2)	20(1)	28(2)	3(1)	2(1)	2(1)
C(6A)	30(2)	22(1)	24(1)	3(1)	2(1)	2(1)
C(7A)	32(2)	18(1)	23(1)	-2(1)	2(1)	3(1)
C(8A)	32(2)	17(1)	27(1)	1(1)	3(1)	4(1)
C(9A)	29(2)	21(1)	22(1)	-3(1)	4(1)	0(1)

C(10A)	30(2)	21(1)	22(1)	-4(1)	4(1)	2(1)
C(11A)	32(2)	21(1)	21(1)	-3(1)	0(1)	3(1)
C(12A)	30(2)	29(2)	27(1)	-3(1)	-1(1)	6(1)
C(13A)	26(2)	34(2)	33(2)	-4(1)	2(1)	4(1)
C(14A)	31(2)	36(2)	29(2)	-5(1)	5(1)	-6(1)
C(15A)	32(2)	23(1)	26(1)	-4(1)	2(1)	1(1)
C(16A)	39(2)	31(2)	36(2)	4(1)	7(1)	-5(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **13i**.

Atom	x	y	z	U(eq)
H(2)	6631	2896	3756	104(19)
H(1)	7422	3459	5359	31
H(2B)	4883	6299	5633	41
H(3)	4072	5124	6347	46
H(4)	4890	3753	6953	44
H(8)	8289	5821	6646	32
H(12)	10648	3260	5436	36
H(13)	11897	4282	5943	39
H(14)	11594	5774	6586	38
H(16A)	9279	6701	6921	50
H(16B)	10192	7153	6544	50
H(16C)	10301	6663	7472	50
H(16D)	10568	6977	7037	50
H(16E)	9656	6525	7414	50
H(16F)	9547	7015	6486	50
H(17A)	7049	1633	2975	56
H(17B)	7949	2267	3373	56
H(18A)	6976	2542	1702	77
H(18B)	8024	2092	1899	77
H(18C)	7837	3221	2099	77
H(1A)	7952	1627	5276	30
H(2A)	10290	-1468	5602	36
H(3A)	11350	-377	6354	41
H(4A)	10780	1032	6972	40
H(8A)	7139	-673	6519	30
H(12A)	4779	2148	5287	35
H(13A)	3543	1267	5772	38
H(14A)	3837	-239	6443	38
H(16G)	6106	-1427	6845	53
H(16H)	5059	-1765	6464	53
H(16I)	5220	-1245	7378	53
H(16J)	4818	-1530	6946	53
H(16K)	5864	-1193	7327	53
H(16L)	5703	-1713	6414	53

Table 6. Dihedral angles [°] for **13i**.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(6) - C(1) - C(2) - C(3)	-0.1(4)
Cl(1) - C(1) - C(2) - C(3)	179.8(2)
C(1) - C(2) - C(3) - C(4)	0.7(4)
C(2) - C(3) - C(4) - C(5)	0.1(4)
C(3) - C(4) - C(5) - C(6)	-1.6(4)
C(3) - C(4) - C(5) - Cl(2)	175.9(2)
C(4) - C(5) - C(6) - C(1)	2.1(4)
Cl(2) - C(5) - C(6) - C(1)	-175.4(2)
C(4) - C(5) - C(6) - C(7)	-176.8(3)
Cl(2) - C(5) - C(6) - C(7)	5.8(4)
C(2) - C(1) - C(6) - C(5)	-1.2(4)
Cl(1) - C(1) - C(6) - C(5)	178.9(2)
C(2) - C(1) - C(6) - C(7)	177.6(3)
Cl(1) - C(1) - C(6) - C(7)	-2.3(4)
C(11) - N(1) - C(7) - C(8)	4.3(4)
C(11) - N(1) - C(7) - C(6)	-174.6(2)
C(5) - C(6) - C(7) - C(8)	-117.3(3)
C(1) - C(6) - C(7) - C(8)	63.9(4)
C(5) - C(6) - C(7) - N(1)	61.6(3)
C(1) - C(6) - C(7) - N(1)	-117.2(3)
N(1) - C(7) - C(8) - C(9)	-0.7(4)
C(6) - C(7) - C(8) - C(9)	178.2(2)
C(7) - C(8) - C(9) - C(10)	-3.1(4)
C(7) - C(8) - C(9) - C(15)	176.7(2)
C(15) - C(9) - C(10) - C(12)	2.4(4)
C(8) - C(9) - C(10) - C(12)	-177.8(2)
C(15) - C(9) - C(10) - C(11)	-176.3(2)
C(8) - C(9) - C(10) - C(11)	3.5(4)
C(7) - N(1) - C(11) - O(1)	177.1(2)
C(7) - N(1) - C(11) - C(10)	-3.8(4)
C(12) - C(10) - C(11) - O(1)	0.2(4)
C(9) - C(10) - C(11) - O(1)	178.9(2)
C(12) - C(10) - C(11) - N(1)	-178.9(2)
C(9) - C(10) - C(11) - N(1)	-0.3(4)
C(9) - C(10) - C(12) - C(13)	-0.6(4)
C(11) - C(10) - C(12) - C(13)	178.1(2)

C(10) - C(12) - C(13) - C(14)	-1.1(4)
C(12) - C(13) - C(14) - C(15)	1.0(4)
C(13) - C(14) - C(15) - C(9)	0.9(4)
C(13) - C(14) - C(15) - C(16)	-177.6(3)
C(10) - C(9) - C(15) - C(14)	-2.5(4)
C(8) - C(9) - C(15) - C(14)	177.7(2)
C(10) - C(9) - C(15) - C(16)	176.0(2)
C(8) - C(9) - C(15) - C(16)	-3.8(4)
C(6A) - C(1A) - C(2A) - C(3A)	-0.4(4)
Cl(1A) - C(1A) - C(2A) - C(3A)	179.4(2)
C(1A) - C(2A) - C(3A) - C(4A)	1.8(4)
C(2A) - C(3A) - C(4A) - C(5A)	-0.9(4)
C(3A) - C(4A) - C(5A) - C(6A)	-1.4(4)
C(3A) - C(4A) - C(5A) - Cl(2A)	175.2(2)
C(4A) - C(5A) - C(6A) - C(1A)	2.7(4)
Cl(2A) - C(5A) - C(6A) - C(1A)	-173.95(19)
C(4A) - C(5A) - C(6A) - C(7A)	-177.0(3)
Cl(2A) - C(5A) - C(6A) - C(7A)	6.4(3)
C(2A) - C(1A) - C(6A) - C(5A)	-1.7(4)
Cl(1A) - C(1A) - C(6A) - C(5A)	178.4(2)
C(2A) - C(1A) - C(6A) - C(7A)	177.9(3)
Cl(1A) - C(1A) - C(6A) - C(7A)	-1.9(4)
C(11A) - N(1A) - C(7A) - C(8A)	2.9(4)
C(11A) - N(1A) - C(7A) - C(6A)	-175.9(2)
C(5A) - C(6A) - C(7A) - C(8A)	-115.8(3)
C(1A) - C(6A) - C(7A) - C(8A)	64.6(4)
C(5A) - C(6A) - C(7A) - N(1A)	63.0(3)
C(1A) - C(6A) - C(7A) - N(1A)	-116.7(3)
N(1A) - C(7A) - C(8A) - C(9A)	-1.7(4)
C(6A) - C(7A) - C(8A) - C(9A)	177.0(2)
C(7A) - C(8A) - C(9A) - C(15A)	178.9(2)
C(7A) - C(8A) - C(9A) - C(10A)	-1.2(4)
C(15A) - C(9A) - C(10A) - C(12A)	2.1(4)
C(8A) - C(9A) - C(10A) - C(12A)	-177.8(2)
C(15A) - C(9A) - C(10A) - C(11A)	-177.0(2)
C(8A) - C(9A) - C(10A) - C(11A)	3.0(4)
C(7A) - N(1A) - C(11A) - O(1A)	178.5(2)
C(7A) - N(1A) - C(11A) - C(10A)	-1.0(4)
C(12A) - C(10A) - C(11A) - O(1A)	-0.7(4)

C(9A) - C(10A) - C(11A) - O(1A)	178.5(2)
C(12A) - C(10A) - C(11A) - N(1A)	178.9(2)
C(9A) - C(10A) - C(11A) - N(1A)	-1.9(4)
C(9A) - C(10A) - C(12A) - C(13A)	-1.4(4)
C(11A) - C(10A) - C(12A) - C(13A)	177.8(2)
C(10A) - C(12A) - C(13A) - C(14A)	0.0(4)
C(12A) - C(13A) - C(14A) - C(15A)	0.5(4)
C(13A) - C(14A) - C(15A) - C(9A)	0.2(4)
C(13A) - C(14A) - C(15A) - C(16A)	-178.5(3)
C(10A) - C(9A) - C(15A) - C(14A)	-1.5(4)
C(8A) - C(9A) - C(15A) - C(14A)	178.4(2)
C(10A) - C(9A) - C(15A) - C(16A)	177.2(2)
C(8A) - C(9A) - C(15A) - C(16A)	-2.8(4)

Table 7. Crystal data and structure refinement for **15b**.

Identification code	k12farm10
Formula weight	265.30
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	$a = 12.5690(8)\text{Å}$ $\alpha = 90^\circ$ $b = 17.0250(11)\text{Å}$ $\beta = 104.837(2)^\circ$ $c = 13.3300(11)\text{Å}$ $\gamma = 90^\circ$
Volume	$2757.3(3)\text{Å}^3$
Z	8
Density (calculated)	1.278 Mg m^{-3}
Absorption coefficient	0.084 mm^{-1}
F(000)	1120
Crystal size	$0.30 \times 0.08 \times 0.08\text{ mm}$
θ range for data collection	$3.52\text{ to }25.03^\circ$
Index ranges	$-14 \leq h \leq 14$; $-20 \leq k \leq 20$; $-11 \leq l \leq 15$
Reflections collected	12394
Independent reflections	4788 [R(int) = 0.1450]
Reflections observed ($>2\sigma$)	1941
Data Completeness	0.982
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.710
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4788 / 0 / 365
Goodness-of-fit on F^2	0.895
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0717$ $wR2 = 0.1299$
R indices (all data)	$R1 = 0.2113$ $wR2 = 0.1699$
Largest diff. peak and hole	0.259 and -0.241 eÅ^{-3}

Notes:

Two independent molecules in the asymmetric unit, which form hydrogen-bonded dimers.

Crystal quality poor - small fragment taken from a non-merohedrally twinned needle. Unit cell parameters reflect the sample quality. However, the structure is unambiguous. Data truncated to 25 degree Bragg angle.

Hydrogen bonds with $H \cdots A < r(A) + 2.000$ Angstroms and $\angle DHA > 110$ deg.

D-H	d(D-H)	d(H...A)	$\angle DHA$	d(D...A)	A
N1-H1	0.880	1.917	168.55	2.785	O1A
N1A-H1A	0.880	2.095	163.52	2.950	O1

Table 8. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 1.U(eq) is defined as one third of the trace of the orthogonallised U_{ij} tensor for **15b**.

Atom	x	y	z	U(eq)
O(1)	4518(2)	1373(1)	-78(2)	50(1)
O(2)	701(2)	3499(1)	-299(3)	76(1)
N(1)	3249(2)	1302(2)	854(2)	42(1)
C(1)	3670(3)	1634(2)	109(3)	46(1)
C(2)	3060(3)	2313(2)	-435(3)	44(1)
C(3)	3416(3)	2679(2)	-1231(3)	53(1)
C(4)	2872(3)	3325(2)	-1706(4)	65(1)
C(5)	1944(4)	3608(2)	-1412(4)	72(1)
C(6)	1590(3)	3260(2)	-636(4)	62(1)
C(7)	2139(3)	2589(2)	-126(3)	48(1)
C(8)	1785(3)	2199(2)	675(3)	53(1)
C(9)	2328(3)	1560(2)	1161(3)	44(1)
C(10)	2011(3)	1117(2)	1975(3)	48(1)
C(11)	1408(3)	1453(2)	2609(4)	68(1)
C(12)	1129(4)	1037(3)	3386(4)	83(2)
C(13)	1447(4)	257(3)	3583(4)	71(1)
C(14)	2019(3)	-74(2)	2953(4)	69(1)
C(15)	2300(3)	331(2)	2160(4)	59(1)
C(16)	1147(4)	-195(3)	4464(5)	117(2)
C(17)	19(4)	4110(3)	-875(4)	103(2)
O(1A)	4580(2)	54(1)	1769(2)	59(1)
O(2A)	8876(2)	-1580(1)	3110(2)	68(1)
N(1A)	6113(2)	279(2)	1218(2)	44(1)
C(1A)	5547(3)	-119(2)	1807(3)	45(1)
C(2A)	6148(3)	-725(2)	2490(3)	48(1)
C(3A)	5629(3)	-1157(2)	3129(3)	54(1)
C(4A)	6200(3)	-1722(2)	3751(4)	59(1)
C(5A)	7298(3)	-1886(2)	3788(3)	59(1)
C(6A)	7818(3)	-1469(2)	3165(3)	56(1)
C(7A)	7252(3)	-868(2)	2501(3)	43(1)
C(8A)	7758(3)	-417(2)	1841(3)	49(1)
C(9A)	7206(3)	148(2)	1208(3)	40(1)
C(10A)	7670(3)	638(2)	512(3)	42(1)
C(11A)	8796(3)	628(2)	582(4)	63(1)
C(12A)	9240(3)	1053(2)	-91(4)	66(1)
C(13A)	8608(3)	1518(2)	-851(4)	58(1)

C(14A)	7495(3)	1542(2)	-908(3)	56(1)
C(15A)	7029(3)	1111(2)	-254(3)	50(1)
C(16A)	9095(3)	1960(2)	-1614(4)	77(1)
C(17A)	9459(3)	-2218(2)	3716(4)	82(2)

Table 9. Bond lengths [Å] and angles [°] for **15b**.

O(1)-C(1)	1.238(4)	O(2)-C(6)	1.369(4)
O(2)-C(17)	1.438(5)	N(1)-C(1)	1.360(4)
N(1)-C(9)	1.395(4)	C(1)-C(2)	1.472(5)
C(2)-C(3)	1.399(5)	C(2)-C(7)	1.405(4)
C(3)-C(4)	1.364(5)	C(4)-C(5)	1.406(5)
C(5)-C(6)	1.363(5)	C(6)-C(7)	1.416(5)
C(7)-C(8)	1.423(5)	C(8)-C(9)	1.357(5)
C(9)-C(10)	1.459(5)	C(10)-C(15)	1.392(5)
C(10)-C(11)	1.394(5)	C(11)-C(12)	1.373(6)
C(12)-C(13)	1.394(6)	C(13)-C(14)	1.360(5)
C(13)-C(16)	1.529(6)	C(14)-C(15)	1.382(5)
O(1A)-C(1A)	1.239(4)	O(2A)-C(6A)	1.364(4)
O(2A)-C(17A)	1.438(4)	N(1A)-C(1A)	1.367(4)
N(1A)-C(9A)	1.394(4)	C(1A)-C(2A)	1.453(5)
C(2A)-C(7A)	1.404(4)	C(2A)-C(3A)	1.406(5)
C(3A)-C(4A)	1.350(5)	C(4A)-C(5A)	1.397(5)
C(5A)-C(6A)	1.377(5)	C(6A)-C(7A)	1.420(5)
C(7A)-C(8A)	1.434(5)	C(8A)-C(9A)	1.348(5)
C(9A)-C(10A)	1.476(5)	C(10A)-C(15A)	1.385(5)
C(10A)-C(11A)	1.395(5)	C(11A)-C(12A)	1.377(5)
C(12A)-C(13A)	1.369(6)	C(13A)-C(14A)	1.382(5)
C(13A)-C(16A)	1.514(5)	C(14A)-C(15A)	1.380(5)
C(6)-O(2)-C(17)	117.7(4)	C(1)-N(1)-C(9)	126.2(3)
O(1)-C(1)-N(1)	121.0(3)	O(1)-C(1)-C(2)	123.2(4)
N(1)-C(1)-C(2)	115.8(3)	C(3)-C(2)-C(7)	121.4(3)
C(3)-C(2)-C(1)	119.8(3)	C(7)-C(2)-C(1)	118.8(4)
C(4)-C(3)-C(2)	119.5(4)	C(3)-C(4)-C(5)	120.0(4)
C(6)-C(5)-C(4)	121.2(4)	C(5)-C(6)-O(2)	125.0(4)
C(5)-C(6)-C(7)	120.1(4)	O(2)-C(6)-C(7)	114.9(4)
C(2)-C(7)-C(6)	117.8(4)	C(2)-C(7)-C(8)	120.3(3)
C(6)-C(7)-C(8)	122.0(4)	C(9)-C(8)-C(7)	121.1(3)
C(8)-C(9)-N(1)	117.8(3)	C(8)-C(9)-C(10)	124.8(3)
N(1)-C(9)-C(10)	117.4(3)	C(15)-C(10)-C(11)	116.5(4)
C(15)-C(10)-C(9)	121.4(3)	C(11)-C(10)-C(9)	122.1(3)
C(12)-C(11)-C(10)	121.9(4)	C(11)-C(12)-C(13)	121.2(4)
C(14)-C(13)-C(12)	116.7(4)	C(14)-C(13)-C(16)	122.7(4)
C(12)-C(13)-C(16)	120.6(4)	C(13)-C(14)-C(15)	123.1(4)
C(14)-C(15)-C(10)	120.5(4)	C(6A)-O(2A)-C(17A)	116.0(3)

C(1A)-N(1A)-C(9A)	125.8(3)	O(1A)-C(1A)-N(1A)	120.5(3)
O(1A)-C(1A)-C(2A)	122.8(3)	N(1A)-C(1A)-C(2A)	116.6(3)
C(7A)-C(2A)-C(3A)	120.9(3)	C(7A)-C(2A)-C(1A)	118.9(3)
C(3A)-C(2A)-C(1A)	120.2(3)	C(4A)-C(3A)-C(2A)	119.3(4)
C(3A)-C(4A)-C(5A)	122.0(4)	C(6A)-C(5A)-C(4A)	119.5(4)
O(2A)-C(6A)-C(5A)	125.5(4)	O(2A)-C(6A)-C(7A)	114.0(3)
C(5A)-C(6A)-C(7A)	120.6(3)	C(2A)-C(7A)-C(6A)	117.8(3)
C(2A)-C(7A)-C(8A)	119.6(3)	C(6A)-C(7A)-C(8A)	122.6(3)
C(9A)-C(8A)-C(7A)	121.8(3)	C(8A)-C(9A)-N(1A)	117.4(3)
C(8A)-C(9A)-C(10A)	125.0(3)	N(1A)-C(9A)-C(10A)	117.6(3)
C(15A)-C(10A)-C(11A)	116.5(3)	C(15A)-C(10A)-C(9A)	122.9(3)
C(11A)-C(10A)-C(9A)	120.6(4)	C(12A)-C(11A)-C(10A)	121.5(4)
C(13A)-C(12A)-C(11A)	122.1(4)	C(12A)-C(13A)-C(14A)	116.4(4)
C(12A)-C(13A)-C(16A)	121.8(4)	C(14A)-C(13A)-C(16A)	121.8(4)
C(15A)-C(14A)-C(13A)	122.5(4)	C(14A)-C(15A)-C(10A)	120.9(3)

Table 10. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **15b**. The anisotropic displacement factor exponent takes the form: $-2 \text{ gpi}^2 [\text{h}^2 \text{ a}^{*2} \text{ U11} + \dots + 2 \text{ h k a}^* \text{ b}^* \text{ U}$

Atom	U11	U22	U33	U23	U13	U12
O(1)	43(2)	49(2)	58(2)	2(1)	12(1)	3(1)
O(2)	82(2)	59(2)	93(3)	16(2)	30(2)	29(2)
N(1)	39(2)	35(2)	49(2)	6(2)	4(2)	2(1)
C(1)	44(2)	41(2)	52(3)	-5(2)	10(2)	-8(2)
C(2)	42(2)	39(2)	47(3)	-4(2)	3(2)	-1(2)
C(3)	61(2)	44(2)	50(3)	5(2)	8(2)	0(2)
C(4)	80(3)	53(3)	62(4)	5(2)	19(3)	3(2)
C(5)	92(3)	56(3)	65(4)	12(2)	17(3)	20(2)
C(6)	70(3)	48(2)	67(4)	0(2)	17(3)	9(2)
C(7)	48(2)	36(2)	55(3)	1(2)	2(2)	3(2)
C(8)	50(2)	47(2)	62(3)	-3(2)	12(2)	5(2)
C(9)	39(2)	45(2)	48(3)	-3(2)	9(2)	-1(2)
C(10)	40(2)	45(2)	59(3)	-6(2)	10(2)	2(2)
C(11)	83(3)	62(3)	62(4)	-2(3)	26(3)	15(2)
C(12)	86(3)	105(4)	68(4)	-2(3)	39(3)	19(3)
C(13)	77(3)	81(3)	64(4)	9(3)	35(3)	6(3)
C(14)	73(3)	64(3)	80(4)	13(3)	39(3)	8(2)
C(15)	57(2)	50(2)	80(4)	2(2)	38(2)	2(2)
C(16)	133(4)	135(5)	112(6)	43(4)	86(4)	29(4)
C(17)	117(4)	91(4)	102(5)	35(3)	30(4)	69(3)
O(1A)	43(2)	59(2)	77(2)	20(2)	19(1)	10(1)
O(2A)	56(2)	73(2)	71(2)	30(2)	10(2)	20(1)
N(1A)	44(2)	35(2)	51(2)	5(2)	11(2)	4(1)
C(1A)	45(2)	40(2)	50(3)	-3(2)	13(2)	-4(2)
C(2A)	50(2)	35(2)	62(3)	2(2)	19(2)	2(2)
C(3A)	58(2)	52(2)	55(3)	4(2)	17(2)	4(2)
C(4A)	70(3)	50(2)	60(3)	11(2)	21(2)	-4(2)
C(5A)	76(3)	48(2)	53(3)	8(2)	16(2)	4(2)
C(6A)	54(2)	51(2)	63(3)	7(2)	16(2)	7(2)
C(7A)	48(2)	38(2)	36(3)	0(2)	-1(2)	4(2)
C(8A)	41(2)	48(2)	57(3)	1(2)	9(2)	0(2)
C(9A)	39(2)	45(2)	32(3)	-8(2)	2(2)	3(2)
C(10A)	41(2)	41(2)	46(3)	-2(2)	12(2)	1(2)
C(11A)	50(2)	63(3)	73(4)	24(2)	11(2)	-4(2)
C(12A)	44(2)	75(3)	74(4)	10(3)	6(2)	-9(2)
C(13A)	57(3)	52(2)	64(3)	9(2)	16(2)	-4(2)

C(14A)	62(3)	55(2)	53(3)	11(2)	18(2)	9(2)
C(15A)	47(2)	50(2)	55(3)	5(2)	15(2)	9(2)
C(16A)	74(3)	87(3)	70(4)	18(3)	20(3)	-10(2)
C(17A)	75(3)	85(3)	84(4)	46(3)	17(3)	35(3)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **15b**.

Atom	x	y	z	U(eq)
H(1)	3591	886	1172	51
H(3)	4032	2478	-1439	63
H(4)	3119	3585	-2236	78
H(5)	1558	4050	-1761	86
H(8)	1157	2389	873	64
H(11)	1183	1986	2499	81
H(12)	712	1286	3798	99
H(14)	2235	-608	3063	83
H(15)	2695	70	1737	71
H(16A)	374	-358	4245	175
H(16B)	1257	144	5076	175
H(16C)	1618	-660	4636	175
H(17A)	436	4602	-799	155
H(17B)	-632	4180	-609	155
H(17C)	-210	3964	-1610	155
H(1A)	5757	651	808	53
H(3A)	4885	-1053	3123	65
H(4A)	5844	-2017	4175	71
H(5A)	7684	-2282	4239	71
H(8A)	8504	-518	1850	59
H(11A)	9268	320	1107	75
H(12A)	10010	1022	-26	79
H(14A)	7033	1868	-1417	67
H(15A)	6257	1139	-330	60
H(16D)	9513	1596	-1935	115
H(16E)	9586	2374	-1247	115
H(16F)	8502	2197	-2152	115
H(17D)	9103	-2716	3453	123
H(17E)	9449	-2151	4443	123
H(17F)	10222	-2223	3662	123

Table 6. Dihedral angles [°] for **15b**.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(9) - N(1) - C(1) - O(1)	177.4(3)
C(9) - N(1) - C(1) - C(2)	-2.0(5)
O(1) - C(1) - C(2) - C(3)	2.2(5)
N(1) - C(1) - C(2) - C(3)	-178.4(3)
O(1) - C(1) - C(2) - C(7)	-176.6(3)
N(1) - C(1) - C(2) - C(7)	2.8(5)
C(7) - C(2) - C(3) - C(4)	1.2(6)
C(1) - C(2) - C(3) - C(4)	-177.6(3)
C(2) - C(3) - C(4) - C(5)	-1.5(6)
C(3) - C(4) - C(5) - C(6)	1.8(7)
C(4) - C(5) - C(6) - O(2)	179.7(4)
C(4) - C(5) - C(6) - C(7)	-1.6(7)
C(17) - O(2) - C(6) - C(5)	7.0(6)
C(17) - O(2) - C(6) - C(7)	-171.8(4)
C(3) - C(2) - C(7) - C(6)	-1.0(5)
C(1) - C(2) - C(7) - C(6)	177.8(3)
C(3) - C(2) - C(7) - C(8)	179.1(4)
C(1) - C(2) - C(7) - C(8)	-2.2(5)
C(5) - C(6) - C(7) - C(2)	1.2(6)
O(2) - C(6) - C(7) - C(2)	-179.9(3)
C(5) - C(6) - C(7) - C(8)	-178.9(4)
O(2) - C(6) - C(7) - C(8)	0.0(6)
C(2) - C(7) - C(8) - C(9)	0.5(6)
C(6) - C(7) - C(8) - C(9)	-179.4(4)
C(7) - C(8) - C(9) - N(1)	0.4(5)
C(7) - C(8) - C(9) - C(10)	-178.8(4)
C(1) - N(1) - C(9) - C(8)	0.4(5)
C(1) - N(1) - C(9) - C(10)	179.8(3)
C(8) - C(9) - C(10) - C(15)	154.8(4)
N(1) - C(9) - C(10) - C(15)	-24.5(5)
C(8) - C(9) - C(10) - C(11)	-25.3(6)
N(1) - C(9) - C(10) - C(11)	155.4(4)
C(15) - C(10) - C(11) - C(12)	1.1(7)
C(9) - C(10) - C(11) - C(12)	-178.8(4)
C(10) - C(11) - C(12) - C(13)	0.5(8)
C(11) - C(12) - C(13) - C(14)	-1.6(7)

C(11) - C(12) - C(13) - C(16)	178.9(5)
C(12) - C(13) - C(14) - C(15)	1.0(7)
C(16) - C(13) - C(14) - C(15)	-179.5(5)
C(13) - C(14) - C(15) - C(10)	0.6(7)
C(11) - C(10) - C(15) - C(14)	-1.7(6)
C(9) - C(10) - C(15) - C(14)	178.3(4)
C(9A) - N(1A) - C(1A) - O(1A)	178.8(3)
C(9A) - N(1A) - C(1A) - C(2A)	0.7(5)
O(1A) - C(1A) - C(2A) - C(7A)	-178.4(3)
N(1A) - C(1A) - C(2A) - C(7A)	-0.4(5)
O(1A) - C(1A) - C(2A) - C(3A)	1.4(6)
N(1A) - C(1A) - C(2A) - C(3A)	179.5(3)
C(7A) - C(2A) - C(3A) - C(4A)	-0.7(6)
C(1A) - C(2A) - C(3A) - C(4A)	179.4(4)
C(2A) - C(3A) - C(4A) - C(5A)	0.7(6)
C(3A) - C(4A) - C(5A) - C(6A)	-0.9(6)
C(17A) - O(2A) - C(6A) - C(5A)	3.8(6)
C(17A) - O(2A) - C(6A) - C(7A)	-175.9(4)
C(4A) - C(5A) - C(6A) - O(2A)	-178.7(4)
C(4A) - C(5A) - C(6A) - C(7A)	1.0(6)
C(3A) - C(2A) - C(7A) - C(6A)	0.9(6)
C(1A) - C(2A) - C(7A) - C(6A)	-179.3(4)
C(3A) - C(2A) - C(7A) - C(8A)	-180.0(4)
C(1A) - C(2A) - C(7A) - C(8A)	-0.1(5)
O(2A) - C(6A) - C(7A) - C(2A)	178.7(3)
C(5A) - C(6A) - C(7A) - C(2A)	-1.1(6)
O(2A) - C(6A) - C(7A) - C(8A)	-0.4(6)
C(5A) - C(6A) - C(7A) - C(8A)	179.8(4)
C(2A) - C(7A) - C(8A) - C(9A)	0.3(6)
C(6A) - C(7A) - C(8A) - C(9A)	179.4(4)
C(7A) - C(8A) - C(9A) - N(1A)	0.0(5)
C(7A) - C(8A) - C(9A) - C(10A)	179.7(3)
C(1A) - N(1A) - C(9A) - C(8A)	-0.6(5)
C(1A) - N(1A) - C(9A) - C(10A)	179.8(3)
C(8A) - C(9A) - C(10A) - C(15A)	168.2(4)
N(1A) - C(9A) - C(10A) - C(15A)	-12.2(5)
C(8A) - C(9A) - C(10A) - C(11A)	-10.0(6)
N(1A) - C(9A) - C(10A) - C(11A)	169.7(3)
C(15A) - C(10A) - C(11A) - C(12A)	-1.4(6)

C(9A) - C(10A) - C(11A) - C(12A)	176.9(4)
C(10A) - C(11A) - C(12A) - C(13A)	1.2(7)
C(11A) - C(12A) - C(13A) - C(14A)	0.1(7)
C(11A) - C(12A) - C(13A) - C(16A)	-177.7(4)
C(12A) - C(13A) - C(14A) - C(15A)	-1.3(6)
C(16A) - C(13A) - C(14A) - C(15A)	176.5(4)
C(13A) - C(14A) - C(15A) - C(10A)	1.2(6)
C(11A) - C(10A) - C(15A) - C(14A)	0.2(6)
C(9A) - C(10A) - C(15A) - C(14A)	-178.0(3)

Section H: Details of the diffraction data and refinement of the structures of complexes of selected isoquinolin-1-ones with tankyrase-2.

Compound	11a	11b	11c	11d	12a	12f
PDB code	4UVL	4UVP	4UVS	4UVT	4UVZ	4UVO
Data						
Beam line	ESRF ID23-1	ESRF ID23-1	ESRF ID14-1	ESRF ID23-1	ESRF ID23-1	ESRF ID23-2
Wavelength (Å)	1.07227	1.07227	0.93340	1.07227	1.07227	0.87260
Space group	C222 ₁	C222 ₁	C222 ₁	C222 ₁	C222 ₁	C222 ₁
<i>Cell dimensions</i>						
a, b, c (Å)	91.30, 97.78, 118.88	91.16, 97.70, 118.69	91.45, 98.68, 119.21	91.54, 97.62, 118.07	91.03, 98.06, 118.03	91.31, 98.25, 119.11
Resolution (Å)	50-2.0 (2.05-2.00)	50-1.75 (1.80-1.75)	50-2.0 (2.05-2.00)	50-1.95 (2.00-1.95)	50-1.60 (1.64-1.60)	50-1.85 (1.90-1.85)
R _{merge}	0.090 (0.706)	0.049 (0.463)	0.080 (0.522)	0.070 (0.597)	0.057 (0.702)	0.071 (0.671)
I / σ I	15.50 (2.85)	16.29 (2.19)	14.48 (2.60)	18.62 (3.37)	20.38 (2.78)	17.10 (2.53)
Completeness (%)	100 (100)	98.4 (85.8)	99.7 (99.9)	99.3 (98.9)	98.4 (97.2)	99.8 (99.9)
Redundancy	7.2 (7.3)	3.5 (2.7)	3.7 (3.7)	7.2 (7.4)	7.3 (7.4)	5.6 (5.6)
Refinement						
R _{work} / R _{free}	0.17253 / 0.21402	0.16841 / 0.20541	0.18164 / 0.21424	0.16868 / 0.21306	0.16365 / 0.18851	0.16633 / 0.19735
<i>B-factors</i>						
Protein	26.6065	21.283	19.9235	26.6735	19.3375	21.6805
Inhibitor	32.4065	19.976	18.473	30.7105	14.0475	26.6415
<i>R.m.s.d.</i>						
Bond lengths (Å)	0.014	0.015	0.013	0.013	0.014	0.015
Bond angles (°)	1.389	1.491	1.305	1.370	1.431	1.441
<i>Ramachandran plot (%)</i>						
Favoured regions	98.53	99.27	98.78	98.78	99.02	99.27
Additionally allowed regions	-	0.57	0.28	0.85	1.13	1.13
Compound	12m	13h	13n	14f	15e	17
PDB code	4UVN	4UVV	4UVU	4UVX	4UVY	4UVW
Data						
Beam line	ESRF ID14-1	Diamond I038	Diamond I038	Diamond I038	Diamond I04-1	ESRF ID23-2
Wavelength (Å)	0.93340	0.976250	0.976250	0.976250	0.92000	0.87260
Space group	C222 ₁	C222 ₁	C222 ₁	C222 ₁	C222 ₁	C222 ₁

<i>Cell dimensions</i>					91.23	97.72	117.81
a, b, c (Å)	90.69, 98.15, 118.0	91.23, 97.72, 117.81	90.23, 98.56, 118.94	90.58, 98.51, 118.50	91.38, 98.36, 119.51	93.56, 96.73, 117.09	
Resolution (Å)	50-2.20 (2.26-2.20)	50-1.90 (1.95-1.90)	30-1.95 (2.00-1.95)	30-1.95 (2.00-1.95)	30-1.95 (2.00-1.95)	50-2.10 (2.15-2.10)	
R _{merge}	0.095 (0.592)	5.7 (70.8)	8.9 (77.3)	8.2 (78.7)	12.3 (94.4)	9.0 (92.6)	
I / σ I	12.85 (2.27)	18.59 (2.45)	12.54 (2.38)	13.60 (2.27)	12.59 (2.07)	17.42 (2.87)	
Completeness (%)	97.1 (99.3)	99.9 (100)	99.9 (100)	99.9 (100)	99.9 (99.9)	99.9 (100)	
Redundancy	3.8 (3.7)	6.7 (6.7)	6.6 (6.6)	6.6 (6.6)	6.7 (6.9)	7.4 (7.5)	
Refinement							
R _{work} / R _{free}	0.18423 / 0.23870	0.16623 / 0.19803	0.1711 / 0.1918	0.1693 / 0.2112	0.1730 / 0.2126	0.1709 / 0.2098	
<i>B-factors</i>							
Protein	20.947	34.8	35.2	36.6	25.6	38.0	
Inhibitor	16.717	27.9	37.0	31.8	33.8	32.2	
<i>R.m.s.d.</i>							
Bond lengths (Å)	0.013	0.011	0.009	0.011	0.009	0.012	
Bond angles (°)	1.354	1.4	1.4	1.4	1.2	1.5	
<i>Ramachandran plot (%)</i>							
Favoured regions	99.02	99.27	98.29	98.53	98.80	98.04	
Additionally allowed regions	0.85	0.73	1.71	1.47	1.20	1.96	

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